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Author(s)	Hosoi, Satoko; Hirata, Yuki; Kurihara, Takumaru et al.
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RESEARCH ARTICLE

Synthesis of Benzo[*c*]azepine-1,3(2*H*)-diones via C–H Alkylation/Cyclization with α,β-Unsaturated Acyl Fluorides

Satoko Hosoi,[a] Yuki Hirata,[a] Takumaru Kurihara,[a] Masahiro Kojima,[a] Tatsuhiko Yoshino,*[a] and Shigeki Matsunaga*[a,b]

Dedicated to Professor Dr. Keiji Maruoka's 70th birthday.

[a] S. Hosoi, Y. Hirata, T. Kurihara, Dr. M. Kojima, Dr. T. Yoshino, Prof. Dr. S. Matsunaga
Faculty of Pharmaceutical Sciences
Hokkaido University
Kita-ku, Sapporo, 060-0812 (Japan)
E-mail: tyoshino@pharm.hokudai.ac.jp; smatsuna@pharm.hokudai.ac.jp

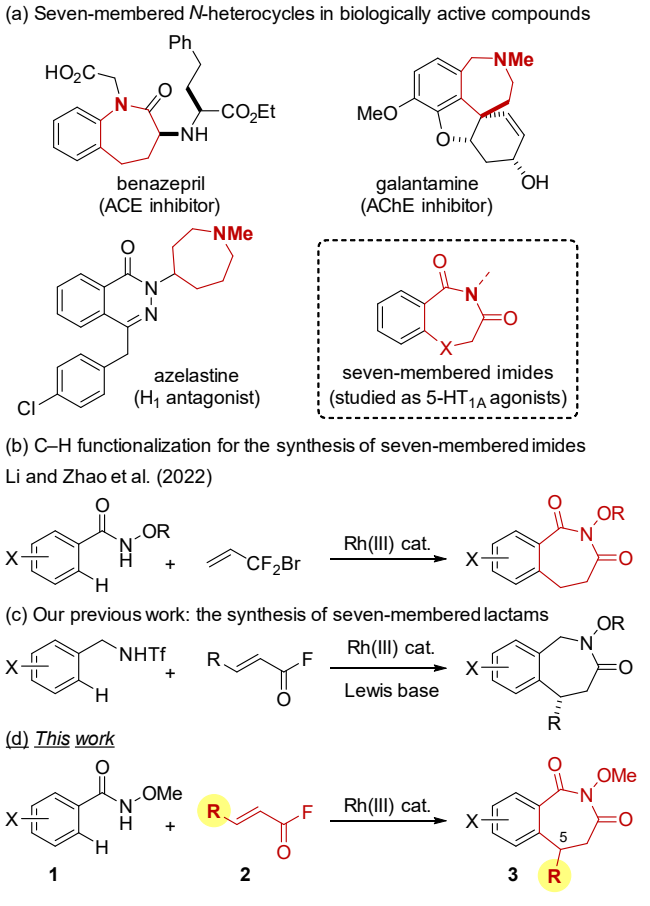
[b] Prof. Dr. S. Matsunaga
Department of Chemistry, Graduate School of Science
Kyoto University
Sakyo-ku, Kyoto, 606-8502
E-mail: smatsuna@kuchem.kyoto-u.ac.jp

Supporting information for this article is given via a link at the end of the document.

Abstract: Transition-metal-catalyzed directed C–H functionalization reactions are a powerful method to construct *N*-heterocycles. However, compared to the formation of five- and six-membered rings, that of seven-membered rings has been much less explored. Here, the synthesis of benzo[*c*]azepine-1,3(2*H*)-diones, which are benzene-fused seven-membered imides, from hydroxamates and α,β-unsaturated acyl fluorides via C–H activation using a Cp*Rh(III) catalyst is described. Under mild reaction conditions, this reaction affords benzo[*c*]azepine-1,3(2*H*)-diones that bear a substituent at the 5-position.

Introduction

Nitrogen-containing heterocyclic structures are ubiquitous in organic compounds, and seven-membered *N*-heterocycles represent a common motif found in numerous biologically active compounds and drug molecules (Scheme 1a).[1,2] For example, benazepril is a nonsulfhydryl angiotensin-converting-enzyme (ACE) inhibitor prodrug used for the treatment of hypertension,[2a] while galantamine is an acetylcholinesterase (AchE) inhibitor used in Alzheimer's disease,[2b] and azelastine is a histamine-H_1-receptor antagonist for the treatment of allergic diseases.[2c] Moreover, seven-membered imides fused with a benzene ring constitute an interesting class of compounds (Scheme 1a, dashed box). Although the literature does not feature many examples of these compounds, they have been studied as selective-serotonin-5-HT_{1A} agonists.[3] Given the success of other similar seven-membered *N*-heterocycles as pharmaceuticals, seven-membered imides would constitute an attractive chemical space to investigate, especially with regards to potential applications in medicinal chemistry. Therefore, we consider efficient synthetic



Scheme 1. Seven-membered *N*-heterocycles and their synthesis via directed C–H functionalization reactions.

routes to such seven-membered imide scaffolds to be of great importance.

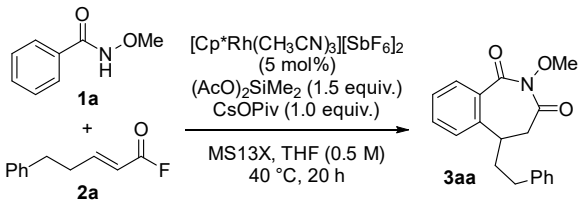
Over the last few decades, transition-metal-catalyzed directed C–H functionalization reactions have attracted great attention as efficient synthetic transformations.[4] In particular, the construction of *N*-heterocyclic structures via the coupling of substrates that bear *N*-containing directing groups with unsaturated reactants has been extensively investigated.[5] However, compared to reactions that generate five- and six-membered rings, those that furnish seven-membered rings have been much less explored.[6-9] As a notable example of the synthesis of seven-membered imides, Li and Zhao have reported the coupling reactions of hydroxamates with 3-bromo-3,3-difluoropropene using a Cp*Rh(III) catalyst to furnish benzo[*c*]azepine-1,3(2*H*)-diones (Scheme 1b).[8] On the other hand, we have recently reported the enantioselective synthesis of seven-membered lactams from benzylamines and α,β-unsaturated acyl fluorides[10] via C–H activation using a Cp*Rh(III) catalyst and a chiral Lewis base (Scheme 1c).[9] With this background in mind, we became interested in the synthesis of benzo[*c*]azepine-1,3(2*H*)-diones **3** from hydroxamates **1** and α,β-unsaturated acyl fluorides **2** via C–H activation, and herein, we report our findings (Scheme 1d). This synthetic route to **3** allows the introduction of a substituent at the 5-position, which expands the diversity of these easily accessible structures.

Results and Discussion

After the examination of various reaction conditions, we found that the reaction of hydroxamate **1a** and acyl fluoride **2a** proceeded in the presence of $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as a catalyst, $(AcO)_2SiMe_2$ as a fluoride scavenger,[11] CsOPiv as a base, and MS13X in THF at 40 °C to afford the desired product (**3aa**) in high yield (Table 1, entry 1). The results of control experiments are summarized in Table 1 (entries 2–10). While omitting $(AcO)_2SiMe_2$ significantly decreased the reactivity (entry 2), the reaction proceeded in moderate yield in the absence of CsOPiv (entry 3), probably because an acetate generated from $(AcO)_2SiMe_2$ can also act as a base. The reactivity decreased moderately when MS13X was removed, or when the reaction was performed at room temperature (entries 4 and 5). While changing the solvent from THF to DCE had only a moderate effect (entry 6), the desired product was not obtained when using MeOH as the solvent (entry 7), probably due to the competitive solvolysis of **2a**. Finally, we evaluated other related transition-metal catalysts, i.e., Cp*Co(III), Cp*Ir(III), and Ru(II), albeit that the desired product was not formed in any of these cases (entries 8–10).

We then examined the substrate scope under the optimized conditions (Scheme 2). Hydroxamates bearing various *para* or *meta* substituents furnished the corresponding products in 41–86% isolated yield (**3aa**–**3ha**). Substrates with an electron-withdrawing group generally exhibited attenuated reactivity (**3da**–**3fa**, **3ha**) compared to substrates with an electron-donating group. The introduction of an *ortho*-methyl group to **1** also decreased the reactivity (**3ia**; 39%). We then investigated other α,β-unsaturated acyl fluorides **2**. In addition to simple linear and branched acyl fluorides (**3ab** and **3ac**), benzyl-ether-substituted acyl fluoride provided the target product in satisfactory yield (**3ad**, 85%).

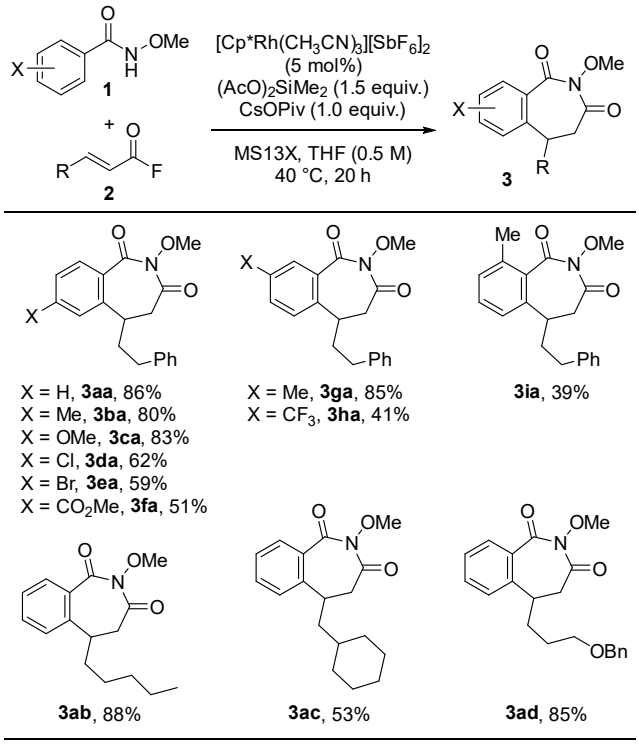
Table 1. Optimized conditions for the C–H alkylation/cyclization of **1a** and **2a** and control experiments [a]



Entry	Deviation from the conditions shown above	%
1	None	94 (86)[c]
2	Without $(AcO)_2SiMe_2$	5
3	Without CsOPiv	47
4	Without MS13X	56
5	At room temperature instead of 40 °C	66
6	In DCE instead of THF	73
7	In MeOH instead of THF	N.D.
8	$Cp^*CoI_2(CO)$ (5 mol %) + $AgSbF_6$ (10 mol %) instead of $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	N.D.
9	$[Cp^*IrCl_2]_2$ (2.5 mol %) + $AgSbF_6$ (10 mol %) instead of $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	N.D.
10	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %) + $AgSbF_6$ (10 mol %) instead of $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	N.D.

[a] Optimized standard reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (0.005 mmol), $(AcO)_2SiMe_2$ (0.15 mmol), CsOPiv (0.10 mmol), and MS13X (20 mg) in THF (0.2 mL) at 40 °C for 20 h. [b] Determined by ^1H NMR analysis of the crude mixture using dibenzyl ether as the internal standard. [c] Isolated yield at a 0.30 mmol (**1a**) scale. N.D. = not detected.

A plausible catalytic cycle is depicted in Figure 1. An active species with carboxylate anions (**I**) can be generated from $[Cp^*Rh(CH_3CN)_3]^{2+}$ and CsOPiv or $(AcO)_2SiMe_2$. The deprotonation and coordination of substrate **1** (**II**) followed by carboxylate-assisted C–H activation forms metallacycle **III**,[12] which further undergoes the coordination and insertion of **2** to furnish intermediate **IV**. After protonation to give **V**, intramolecular nucleophilic substitution between the hydroxamate moiety and acyl fluoride provide **3**. The fluoride anion can be trapped by $(AcO)_2SiMe_2$, regenerating the active catalyst (**I**).



Scheme 2. Substrate scope.

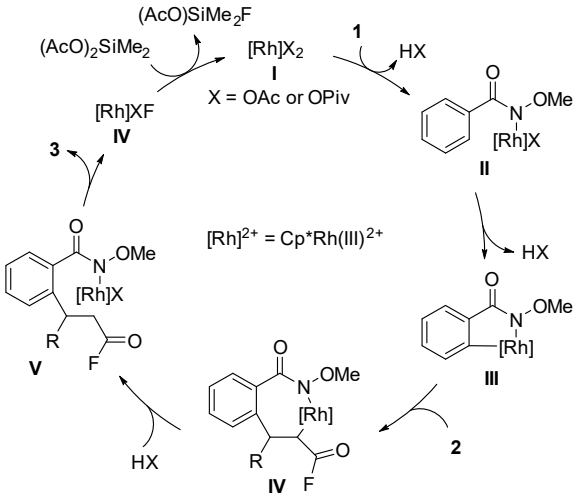


Figure 1. Plausible catalytic cycle for the formation of benzo[*c*]azepine-1,3(2*H*)-diones (**3**) from hydroxamates (**1**) and α,β-unsaturated acyl fluorides (**2**) via C–H activation.

Conclusion

In summary, we have demonstrated that the coupling reactions of hydroxamates (**1**) and α,β-unsaturated acyl fluorides (**2**) via Rh(III)-catalyzed C–H activation efficiently furnish benzo[*c*]azepine-1,3(2*H*)-diones (**3**) under mild reaction conditions (THF, 40 °C). Our findings can be expected to open new opportunities for the application of seven-membered imide scaffolds in medicinal chemistry and the discovery of biologically active molecules.

Acknowledgements

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Keywords: C–H activation • α,β-unsaturated acyl fluoride • hydroxamate • imide • benzo[*c*]azepine-1,3(2*H*)-dione

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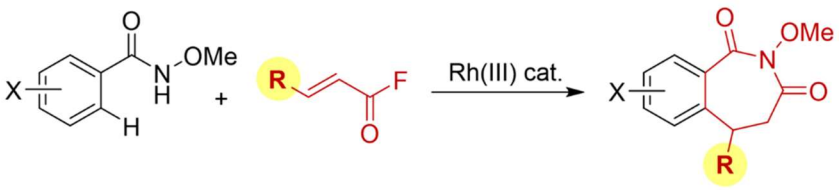

Rh(III)-catalyzed C–H alkylation/cyclization reactions of hydroxamates and α,β-unsaturated acyl fluorides are described. Optimized mild reaction conditions using a $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ furnish benzo[*c*]azepine-1,3(2*H*)-diones bearing a substituent at the 5-positions.

Institute and/or researcher Twitter usernames: @MatsunagaGroup