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SPECIAL FEATURE: BRIEF COMMUNICATION

Re(I)-catalyzed hydropropargylation of enamides: a useful method for the preparation of 4-pentynylamine derivatives

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Abstract

Hydropropargylation of enamides was achieved in good yields through the 1,4-addition of enamides to the α,β-unsaturated carbene complex intermediate, followed by intramolecular hydrogen transfer to the iminium carbon. This method is useful for the synthesis of 4-pentynylamine derivatives from enamides and easily available propargyl ether. Moreover, tandem cyclization reaction was achieved to afford a pyrrolidine derivative in a single operation by using a secondary enamide.

Introduction

4-Pentynylamine derivatives have been employed not only as a useful synthetic intermediate for preparation of various biologically important compounds such as pyrrolidine and piperidine derivatives [1–8], but also as a connecting unit of biologically active compounds through click chemistry [9–12]. Most of these compounds were synthesized by the conventional substitution reaction of 4-pentynyl halides with nitrogen nucleophiles [13, 14] or the reduction of the 4-pentynoyl amides [8], but these protocols sometimes require harsh conditions and functional group compatibility is also limited.

We previously reported the $ReI(CO)_5$-catalyzed generation of α,β-unsaturated carbene complex intermediates from propargyl ethers and applied it to the reaction with siloxydienes to give cycloheptadiene derivatives [15]. This reaction was further extended to the $ReI(CO)_5$-catalyzed hydropropargylation reaction of silyl enol ethers with propargyl ethers to give 4-pentynol derivatives [16]. In this paper, we report further expansion of this methodology to the reaction of enamides instead of silyl enol ethers to give synthetically useful 4-pentynylamine derivatives, which proceeds under neutral conditions using just a catalytic amount of a transition metal complex.

The choice of the substituent on the nitrogen atom was examined first using propargyl diphenylmethyl ether **1** as a precursor of α,β-unsaturated carbene complex intermediate according to the similar procedure for the reaction with silyl enol ethers (Table 1, **A**) [16]. While the reaction of pyrrolidine enamine of cyclohexanone **2b** or β,β-dimethyl-substituted enimide derived from phthalimide **2c** did not give the product at all, the reaction of β,β-dimethyl-substituted enamide derived from pyrrolidone **2a** [17] gave the desired hydropropargylation product **3a** in good yield. The enamide **2a** is thought to retain sufficient nucleophilicity compared to enimide **2c** without suppressing the catalytic activity of the Re catalyst due to the lower basicity compared to enamine **2b**. Thus, by heating a mixture of enamide **2a** and two equivalents of propargyl diphenylmethyl ether **1** in the presence of 6 mol% amount of $ReI(CO)_5$ at 100 °C in dioxane for 10 h, the desired hydropropargylation product **3a** was obtained in 71% yield. Use of other $ReX(CO)_5$ (X = Cl, Br) catalysts or other solvents lowered the yield considerably.

The generality of the reaction was examined concerning the substituent on the nitrogen atom (Table 1, **A**), and enamides of cyclic amides, such as piperidone and oxazolidone, were found to give the corresponding products **3e** and **3 f** in moderate to good yields while enamide of acylic amide **2d** turned out to be unapplicable. Next the substituent

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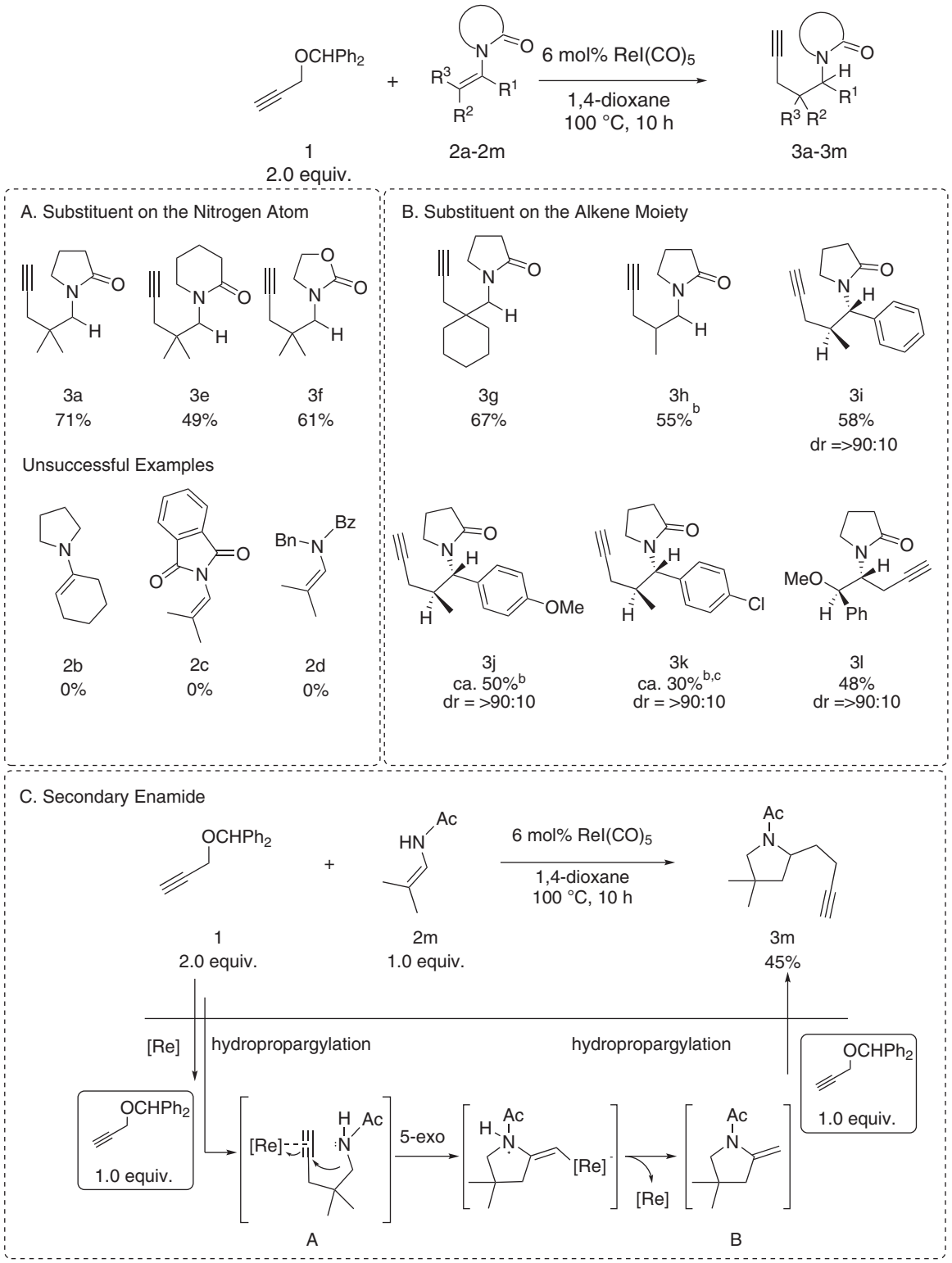
Table 1 Generality of Substrate[a]



[a]Isolated yield based on enamide

[b]NMR yield

[c]MS3A was added

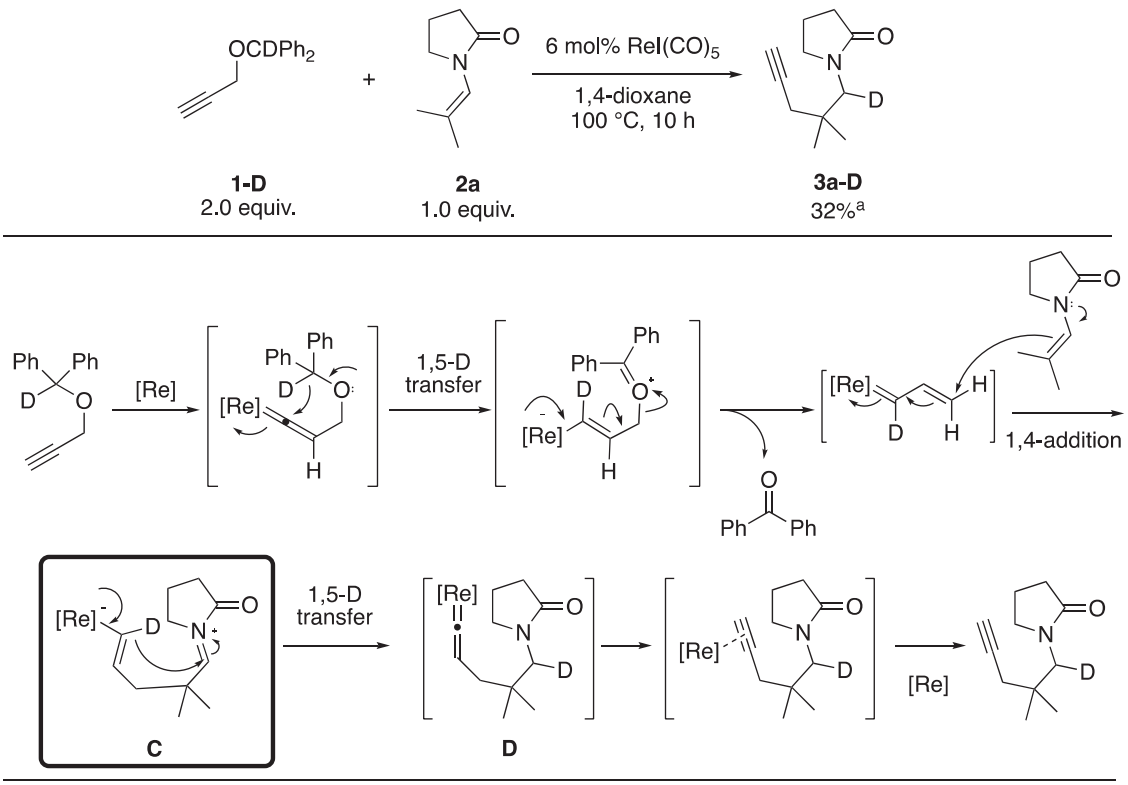


Fig. 1 Deuterium experiment and proposed reaction mechanism

on the alkene moiety was examined using enamides derived from pyrrolidone (Table 1, **B**). It was found that cyclohexylidene enamide also gave the corresponding substituted 4-pentynylamine derivatives **3 g** in a reasonable yield. α,β-Disubstituted enamides also gave the products **3i~k** with high diastereo-selectivity. In these reactions, the enamides of (*E*)-geometries (*E*: *Z* ≥ 90: 10) were employed [17], but as the diastereoselectivity is determined at the stage of the 1,5-hydrogen transfer step, the high diastereoselectivity is thought to be realized due to the restricted transition state of the intramolecular hydrogen transfer (See Fig. 1). The structure of **3i** was determined by single crystal X-ray analysis of its dimerized product obtained by the coupling reaction of the terminal alkyne. Interestingly, β-methoxy-substituted enamide gave the product **3l** in which the propargyl substituent was introduced to the carbon substituted with the amido group. This implies that β-methoxy enamide actually worked as an enol ether nucleophile instead of enamide. Again the product was obtained with high diastereoselectivity starting from (*Z*)-enamide. The structure of **3 l** was determined by the single crystal X-ray analysis.

When a secondary enamide **2 m** was employed, a contiguous hydropropargylation-cyclization-hydropropargylation reaction was found to proceed in a reasonable yield (Table 1, **C**). Treatment of a secondary enamide **2 m** with two equivalents of **1** gave pyrrolidine derivative **3 m** in 45% yield. The reaction first gave the hydropropargylation intermediate **A**, which underwent 5-exo cyclization of the amide nitrogen onto the terminal alkyne to give another enamide **B** through electrophilic activation of the alkyne moiety by the Re catalyst. This further underwent another hydropropargylation reaction to give the final product **3 m**. Thus, a synthetically useful pyrrolidine derivative with an unsaturated sidearm was prepared in a simple single operation. Pyrrolidine derivative **3 m** could be a useful precursor for the preparation of pyrrolizidine alkaloids, which are widely found in nature as a biologically active compounds [18, 19], by further intramolecular addition reaction of the nitrogen towards the alkyne moiety.

The reaction was thought to proceed in a similar manner to the previous reaction with silyl enol ethers [16, 20]. First, α,β-unsaturated carbene complex intermediate is generated from the propargyl ether and then enamides add to this complex in a 1,4-addition manner to give alkenylrhenium intermediate **C**. The 1,5-hydrogen transfer of the hydrogen atom of the alkenylrhenium moiety to the iminium carbon generates vinylidene complex **D**, which liberates the product with regeneration of the rhenium catalyst. This mechanism was supported by the deuterium labelling experiments as shown in Fig. 1. Starting from the propargyl ether **1-D** deuterated at the diphenyl-substituted carbon, 4-pentynylamine derivatives **3a-D** deuterated at the α-position of nitrogen atom was obtained with complete deuteration.

In conclusion, a concise method for preparation of 4-pentynylamine derivatives, which are useful intermediates for the synthesis of nitrogen containing compounds, is developed starting from enamides and a propargyl ether. By using a secondary enamide, consecutive reactions proceeded to afford a pyrrolidine derivative in a single operation. Further application of this methodology to the preparation of biologically active compounds is now in progress.

Experimental

General procedure of hydropropargylation of enamide

A mixture of $ReI(CO)_5$ (5.4 mg, 0.012 mmol, 6 mol%), enamide **2** [17] (0.2 mmol, 1.0 equiv.) and propargyl ether **1** (88.9 mg, 0.4 mmol, 2.0 equiv.) in 1,4-dioxane (1.0 ml) was stirred for 10 h at 100 °C under a N_2 atmosphere. The reaction mixture was quenched by addition of TMEDA (0.2 ml) and was concentrated under reduced pressure in vacuo. The crude material was purified by silica-gel column chromatography (ethyl acetate/hexane = 1/3) to give the corresponding product.

Crystallographic data of compounds **3i-dimer** and **3 l** have been deposited in the Cambridge Crystallographic Data Centre as CCDC 1883232 for **3i-dimer** and CCDC 1883244 for **3j**. The data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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