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A Method for Cleaving an Allyl Protecting Group at the Amide Nitrogen of Peptides by One-Pot Olefin Isomerization−Oxidation

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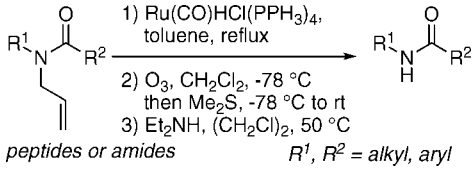
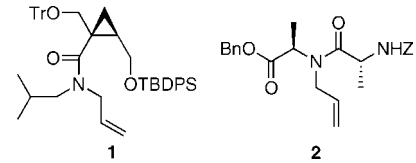


A facile method for *N*-deallylation at the amide nitrogen of peptides is described. One-pot deallylation of a substrate through ruthenium hydride-catalyzed terminal olefin isomerization and subsequent ozonolysis gave the corresponding deallylated product under mild conditions.

The proper selection of efficient protecting groups and the search for selective deprotection methodologies are still crucial issues in modern organic chemistry. Protective groups on heteroatoms such as nitrogen and oxygen are particularly important, and the use of an allyl group to protect a nitrogen atom of amines and amides is becoming increasingly popular, since in contrast to classical protecting groups such as carbamates, amides, and sulfonamide, it is inert under both acidic and basic conditions.[1] Furthermore, an ally group is less hindered and accordingly can easily protect nitrogens, even those with significantly bulky neighboring groups. In fact, cleaving of an allyl protecting group in amines is a well-documented methodology, especially with the use of π-allyl palladium catalysis and ruthenium or rhodium hydride complexes.[2]

In our work on medicinal chemistry with cyclopropane as a key conformationally restricted unit,[3] we prepared functionalized amides, such as **1** (Figure 1), using an allyl group as a protecting group for an amide nitrogen to address a serious problem in its removal from *N*-allylated amides. Although we examined a variety of protecting groups on the amide nitrogen, none of them, except for the allyl group, could be introduced, probably due to the steric demand of the substrate. We also encountered the same problem in an *N*-allylated peptide **2**, with many more functional groups. Some natural and unnatural peptides are important with regard to their biological functions, sequences, sites of action, and the strategies used to improve their pharmacological properties.[4] We report here the first successful development of a facile protocol for the *N*-deallylation of peptides under mild conditions. This is a one-pot deallylation via ruthenium-catalyzed isomerization and subsequent ozonolysis.



1 **2**

FIGURE 1. An amide **1** and a peptide **2** with some functional groups.

Despite its great synthetic interest, the deprotection of *N*-allylic amides, especially peptides, has been relatively unexplored. Initially, we attempted the *N*-dellaylation of **1** and **2** using previously reported procedures.[5] However, with the use of Rh catalysis, such as $RhCl(PPh_3)_3$[5a,b,d] and $RhCl_3$,[5a,c,e] Pd catalysis,[5f,g] an Al−Ni(cat.) system,[5h] $Fe(CO)_5$,[5i] Ir catalysis,[5j] and Ru catalysis, **2** was recovered or decomposed, and none of the desired *N*-deallylated product was obtained. Oxidative cleave[5p] and traditional basic conditions[5q−s] also did not work for the *N*-deallylation of **2**.

On the basis of these miserable results, we considered some of the above methods that involve initial isomerization of the carbon−carbon double bond of the allyl unit and subsequent oxidative cleavage of the resulting enamide. Recently, we reported the selective isomerization of *N*-allylated amide, carbamate, and sulfonamide with the combination of second-generation Grubbs catalyst and electron-rich olefin, such as vinyloxytrimethylsilane or vinyl ethyl ether,[6] where ruthenium hydride generated in situ was identified as the actual active species of this reaction.[7] Through the research, we also demonstrated that a ruthenium hydride, $Ru(CO)HCl(PPh_3)_4$,

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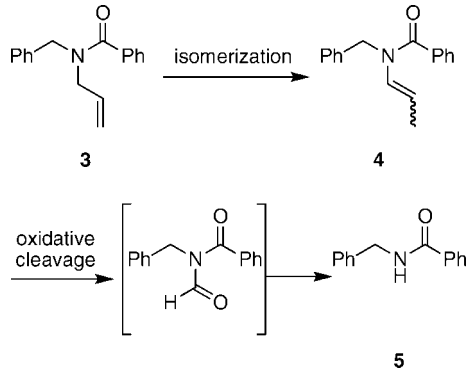
SCHEME 1. Our *N*-Deallylation of Amide 3



effectively catalyzes the isomerization of terminal olefins to give the isomerized products in high yields.

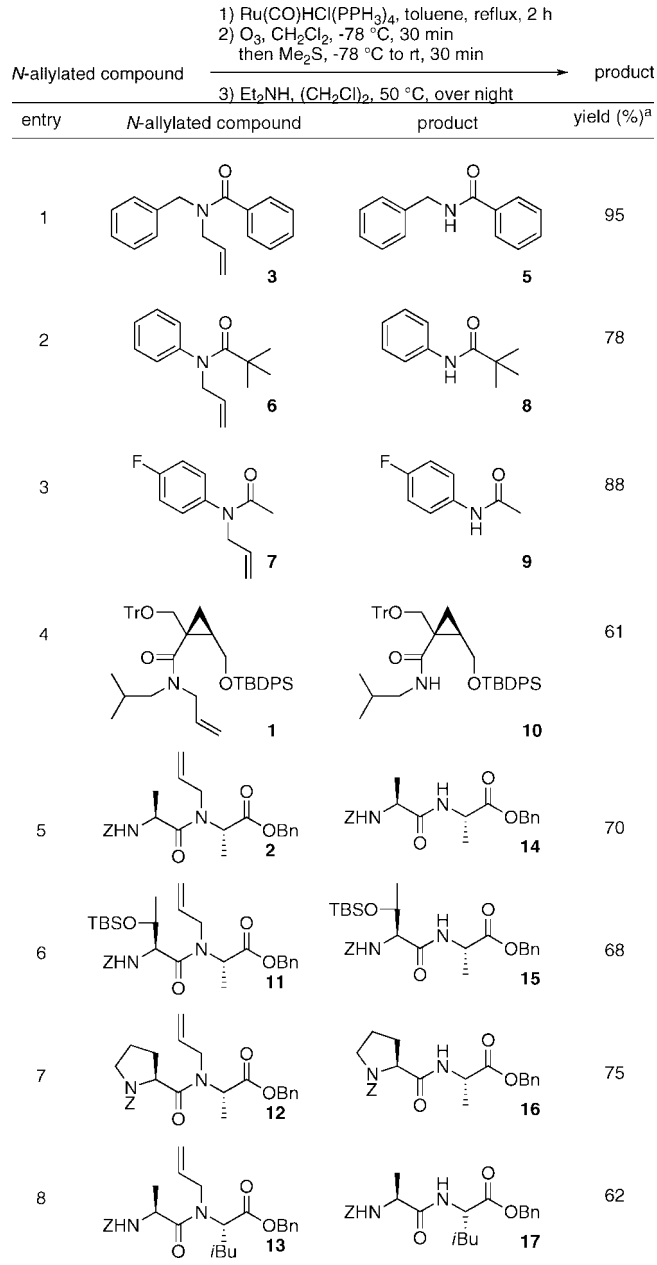
Therefore, we thought that, with $Ru(CO)HCl(PPh_3)_4$ as an olefin isomerization catalyst, we could develop an efficient method for the *N*-deallylation of amides with various functional groups including peptides by the combining it with the subsequent oxidation (Scheme 1). Thus, we planned to examine the reaction of this catalysis with **3** as a model substrate.

Thus, a solution of **3** and 5 mol % of $Ru(CO)HCl(PPh_3)_4$ in toluene was refluxed for 2 h to give the expected **4** quantitatively as a mixture of *cis* and *trans* isomers. Without purification of the product **4**, subsequent standard ozonolysis gave the corresponding stable *N*-formyl intermediate, which was readily hydrolyzed under basic conditions to yield **5** [95% yield from **3** (3 steps), Table 1, entry 1]. With the same method, *N*-allyl groups at other amides (**6** and **7**) were cleaved to yield **8** and **9** in respective yields of 78% and 88% (3 steps) (entries 2 and 3). It should be noted that the deallylation of the sterically hindered *N*-allylated amide **1** with functional groups also proceeded in 61% yield, which has not been achieved by conventional methods (entry 4).

With these results in hand, we then examined the present one-pot protocol for the deallylation of peptide **2** (entry 5). As a result, the expected **14** was obtained in good yield without racemization. The reaction can tolerate a wide range of steric and electronic environments. The reaction of **11**−**13** gave the corresponding deallylated peptides (**15**−**17**) without any problems in respective yields of 68%, 75%, and 62% (entries 6−8). This kind of effective *N*-deallylation protocol for peptides has not yet been reported, and therefore this method may be useful in the synthesis of compounds with amide groups including peptides.

In conclusion, we have developed a one-pot deallylation through facile isomerization and ozonolysis that worked well for *N*-allylated amides with functional groups, such as *N*-allylated peptides. The isomerization of *N*-allyl amides was promoted by $Ru(CO)HCl(PPh_3)_4$ catalyst, and ozonolysis of the enamide directly produced the desired *N*-deallylated amide via an *N*-formyl intermediate. Although allyl groups offer several advantages compared to classical protecting groups for protecting amides even under steric crowding, there have been problems with their cleavage. Thus, this method may make allyl groups effective as useful protective groups on peptides and functionalized amides.

TABLE 1. *N*-Deallylation of Amides (1, 3, 6, and 7) and Peptides (2 and 11−13)



[a] Isolated yield (3 steps).

Experimental Section

General Procedure for Deallylation of an *N*-Allylated Peptide or Amide. To a solution of an *N*-allylated substrate in toluene (0.1 M) was added $Ru(CO)HCl(PPh_3)_4$ catalyst (5 mol%) under an Ar atmosphere. The mixture was refluxed for 2 h. After removal of the solvent, the residue was diluted in CH_2Cl_2 (0.05 M) and cooled to −78 °C. After bubbling of O_3 gas into the mixture for 30 min O_3 was substituted with Ar. To the mixture was added Me_2S (10 equiv), then the whole was warmed to room temperature and solvent was removed. To a solution of residue in $(CH_2Cl)_2$ (0.1 M) was added Et_2NH (3 equiv) and the mixture was refluxed overnight. After removing the solvent the residue was purified by

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column chromatography on silica gel to give the corresponding deallylated product.

***N*-Benzoylbenzylamine (5):**[8] yield, 95% from **3**, a colorless needle; mp 107−108 °C from hexane/AcOEt (lit. mp 104−105 °C from MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80−7.78 (2 H, d, J = 7.3 Hz), 7.48 (2 H, t, J = 7.3 Hz), 7.34 (4 H, d, J = 4.1 Hz), 7.30(1 H, m, aromatic), 6.56 (1 H, br s), 4.63 (2 H, d, J = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.32, 138.14, 134.31, 131.49, 128.73, 128.54, 127.86, 127.55, 126.92, 44.05; LRMS (EI) *m*/*z* 105 (100%, base peak), 211 (26%, M^+).

***Z*-Ala-Ala-OBn (14):**[9] yield, 70%, a colorless powder; mp 139−142 °C (lit. mp 139 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.35 (10 H, m), 6.52 (1 H, broad), 5.34 (1 H, broad), 5.21−5.11 (4 H, m), 4.60 (1 H, m), 4.24 (1 H, br s), 1.41−1.36 (6 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.48 171.70, 155.87, 136.14, 135.20, 128.63, 128.54, 128.49, 128.20, 128.17, 128.08, 67.24, 67.04, 50.41, 48.19, 18.58, 18.25; LRMS (EI) *m*/*z* 91 (100%, base peak), 384 (%, M^+); $[\alpha]^{23}_D$ −23.3 (*c* 2.0, $CHCl_3$) [lit.[10] $[\alpha]^{22}_D$ −20.9 (*c* 2.0, $CHCl_3$)].

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Supporting Information Available: Experimental procedures and full characterizations of compounds **1**, **2**, **5**, and **8**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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