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Zinc mediated Barbier type propargylation of cyclic imides

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Abstract

Propargylations of cyclic imides such as *N*-benzylsuccinimide and *N*-methylsuccinimide were accomplished under mild Barbier type conditions using zinc metal, propargyl bromides and catalyst. The use of $PbBr_2$ is essential to ensure the completion of the reaction to provided propargylated γ-hydroxylactams in high yields without the recovery of cyclic imides.

Keywords: propargylation; cyclic imide; Barbier; zinc; propargyl bromide; γ-hydroxylactam.

Recently, Barbier type allylation and propargylation reactions using zinc,[1] indium, tin,[2] copper,[3] and gallium[4] are gathering attention. Most of these reactions are carried out with aldehyde, imines[1f] and ketones. Additionally, it is reported that the Zn–Barbier reaction of carbonyl compounds with propargyl halides in aqueous medium give homopropargylic alcohols in moderate yields, with the recovery of unreacted aldehydes and a small amount of allenic products.[1c] These Barbier type reactions, with relatively less reactive cyclic imides, have not been reported in the literature to our knowledge. The only example of this type of reaction reported in the literature is intramolecular Reformatsky reaction.[5] It is well known that reactive organometallic compounds such as alkyllithium and Grignard reagents react with cyclic imides to give alkylated hydroxylactam products in moderate yields, together with ring opened products.[6] The unprecedented Barbier type reaction of cyclic imide itself is of great interest.

Here, we found a very efficient synthetic method for the preparation of propargylated γ-hydroxylactam compounds **3** under zinc mediated Barbier condition. The reaction of succinimide derivatives with 2 equiv. of propargyl bromide and 3 equiv. of activated zinc,[7] without any catalyst, gave moderate yield of γ-hydroxylactams with the recovery of starting material. Our attempts using Lewis acid such as $ZnCl_2$, $MgBr_2$, $TiCl_4$, $SnCl_4$ and $BF_3{\cdot}Et_2O$ resulted in low to medium yield of desired products. Fortunately, the use of 10 mol percent of $PbBr_2$ promoted the reaction to completion. The use of $PbBr_2$ as catalyst was essential in our syntheses. At present, the role of $PbBr_2$ is not yet elucidated. However, we think that our work is closely related with in situ

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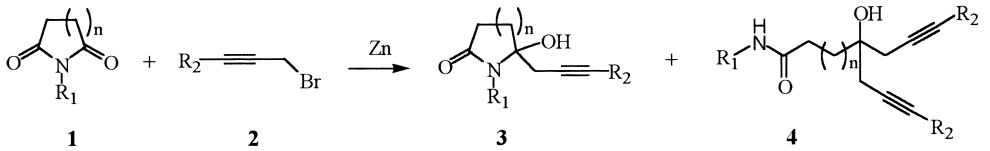
generated allyllead reagent, which was formed by treatment of allyl bromide with aluminum and catalytic amount of $PbBr_2$.[8] It was reported that the use of chemically activated zinc increased the yields of Reformatsky reaction[7a,b] and pulsed sonoelectrochemically produced zinc powder, greatly increased the yield of Barbier type allylation reaction.[7c] However, zinc granule purchased from Aldrich without further activation gave good results in our experiments. In the case of larger cyclic imides such as *N*-benzylglutarimide and *N*-benzyladipimide, major products were ring-open disubstituted alcohol compound **4**. Since *N*-benzylglutarimide adduct was found ring-open extremely toward keto-amide,[6e] which is more reactive toward propargylation than glutarimide, compounds **4** were obtained as major products. Also, it was found that propargylation of acyclic imides such as *N*-benzyldiacetamide and *N*-benzyldicarproamide, with trimethylsilylpropargyl bromide, afforded exclusively 4-alkyl-1,7-bis(trimethylsilanyl)hepta-1,6-diyn-4-ol. These results are summarized in Table 1.

Table 1
Zinc mediated Barbier type propargylation of cyclic imides[a]



1 **2** **3** **4**

$R_1 = CH_3$, benzyl, R_2 = TMS, CH_3, H, n = 0, 1, 2

Entry	Cyclic Imides	R_1	R_2	Reaction time / h	Isolated yield **3**	Isolated yield **4**
1	n = 1	Bn	TMS	18	94	-
2	n = 1	Bn	CH_3	10	45	-
3	n = 1	Bn	H	24	88	-
4	n = 1	CH_3	TMS	20	95	-
5	n = 1	CH_3	CH_3	12	62	-
6	n = 1	CH_3	H	6	90	-
7	n = 2	Bn	TMS	20	-	51
8	n = 2	Bn	H	24	-	45
9	n = 3	Bn	TMS	12	-	72

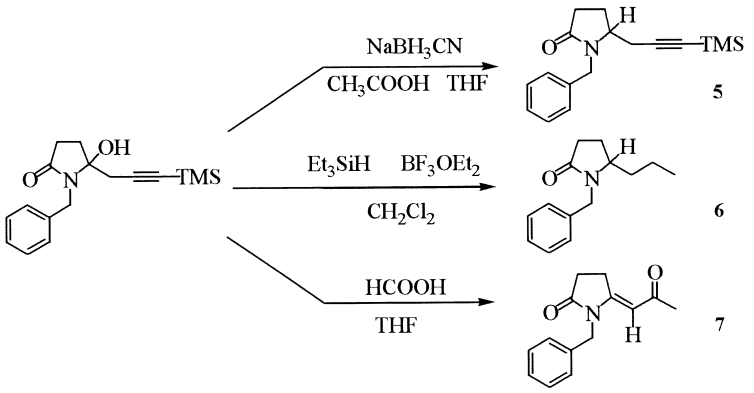
a; All reactions were carried out 2.5 –5 mmol scale at room temperature.

Typical reaction procedures are as follows; To a mixture of *N*-benzylsuccinimide (5 mmol), zinc granule (10 mmol) and $PbBr_2$ (0.5 mmol) in THF (3 mL), was added trimethylsilylpropargyl bromide (7 mmol), slowly over 30 min. The reaction mixture was stirred at room temperature until it became sticky greenish-gray slurry. To the reaction mixture were added another portion of THF (7 mL) and propargyl bromide (3 mmol). The reaction was checked using ^1H NMR. The reaction mixture was quenched with saturated NH_4Cl solution (30 mL), then extracted with ethyl acetate (2×50 mL). The ethyl acetate solution was washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated to give **3**. Crude **3** was recrystallized from the mixture of ethyl

acetate and hexane to give pure **3** (1.321 g, 4.38 mmol).[9] Flash column chromatography of mother liquor provided another crop of pure **3** (0.097 g, 0.32 mmol). An attempt to purify the crude product by silica gel chromatography led to slight decomposition.

In Zn–Barbier reaction of carbonyl compounds with propargyl bromide and trimethylsilylpropargyl bromide in anhydrous THF, homopropargylic alcohols were obtained as major products,[1c,10] while allenic alcohols were obtained as major products with 1-bromo-2-butyne.[1c] The reactions of 1-bromo-2-butyne with *N*-methylsuccinimide and *N*-benzylsuccinimide were not clean, as expected. About 20% of allenic products were observed from the ^{1}H NMR of crude products.

There are many reports on the reaction of γ-hydroxylactams.[6,11] In order to check the versatility of our propargylated γ-hydroxylactams, 1-benzyl-5-hydroxy-5-(3-trimethylsilylprop-2-ynyl)-pyrrolidin-2-one was reduced with $NaBH_3CN$ to give 1-benzyl-5-(3-trimethylsilylprop-2-ynyl)-pyrrolidin-2-one in 81% yield. When triethylsilane was used as the reducing agent, fully reduced product **6** was obtained. Prolonged exposure of this compound to weak acid afforded 1-benzyl-5-(2-oxopropylidene)pyrrolidin-2-one[12] (Scheme 1). From the results of the above preliminary experiments, the reactions of propargylated γ-hydroxylactams were regarded to proceed via *N*-acyliminium intermediate without the tautomerization to keto-amides.



Scheme 1. Reactions of 1-benzyl-5-hydroxy-5-(3-trimethylsilylprop-2-ynyl)pyrrolidin-2-one

Because γ-hydroxylactam derivatives are precursors of acyliminium ions, which are capable of the introduction of other alkyl groups, further synthetic application in organic synthesis are under investigation. The allylation of cyclic imides with the same method was also carried out to give similar results in lower yields compared to propargylation (35 to 70% isolation yields). These allylation reactions did not show advantages over the conventional method. Therefore, we are making a lot of efforts to improve the yields of allylated hydroxylactams.

Acknowledgements

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9. Entry 1 in Table 1: mp 90–92°C, ^{1}H NMR (400 MHz, $CDCl_3$,): δ 0.13 (s, 9 H), 2.0–2.1 (m, 1 H), 2.40–2.60 (m, 5 H), 3.43 (s, 1 H), 4.50 (dd, 2 H, J = 5.4 Hz), 7.13–7.34 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 0.24, 29.8, 32.1, 33.8, 42.9, 89.0, 91.5, 100.8, 127.7, 128.4, 128.9, 138.4, 175.5; MS, m/e 301 (M^+).
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12. The stereochemistry for the double bond of **7** was confirmed to by NOE experiments. When the vinyl hydrogen was saturated, the signals from the NCH_2 and CH_3 showed NOE (2.6 and 1.8%), but the 4-H signals were not enhanced. Also, when the NCH_2 was saturated, the signals from the vinyl hydrogen showed NOE (13.5%).