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Synthesis of 4-allenyl and 4-proparyl-2-azetidinone via Zn-mediated Barbier-type reaction and Pt-catalyzed intramolecular amidation to carbapenem skeletons

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Abstract—4-Propargyl-2-azetidinone and 4-allenyl-2-azetidinone derivatives can be facilely obtained from 4-acetoxy-2-azetidinone and propargyl bromides via zinc-mediated Barbier-type reaction. A new method has been developed to construct the carbapenem bicyclic nucleus by cyclization of 4-propargyl-2-azetidinone and 4-allenyl-2-azetidinone derivatives catalyzed by $PtCl_2$.

Since the discovery of thienamycin and related carbapenem antibiotics,[1] carbon–carbon bond formation at C4-position of 2-azetidione has attracted much attention in the field of organic synthesis.[2] In addition, the use of 2-azetidione as a chiral building block in organic synthesis is well documented.[3] Among the various C4-position functionlized products of 2-azetidione, the allenyl and propargyl derivatives are particularly attractive due to their high reactivity and the three-carbon unit for the elaboration to carbapenem framework.[4] They have been prepared by the addition of propargyl or allenyl organometallic reagents of magnesium,[5] silicon,[6] tin,[7] and zinc[8] to 4-acetoxy-2-azetidinone or 4-sulfonyl-2-azetidinone derivatives, assuming imine equivalents.[9] The other methods involve nucleophilic addition of alkynylmetal reagents to the aldehyde, ketone, or Weinreb amide. Nevertheless, the rigorous conditions for most of the organometallic reagents limit their utilities.

Very recently, Lee and co-workers[10] discovered the selective introduction of allenyl and propargyl groups at the C4-position of 2-azetidinones with propargyl bromide via indium-mediated reaction. Although this methodology is advantageous in yield, it suffers many limitations such as moderate selectivity of synthesizing versatile terminal alkyne product, a lot of colloid in the work-up procedure, and the availability of indium. The development of cheap organometallic reagents and practical methods with discrepant selectivities is still highly desirable. Herein, we report a general strategy utilizing Zinc-mediated Barbier-type reaction of propargyl bromides with 4-acetoxy-2-azetidinone, to afford 4-allenyl-2-azetidinone and 4-propargyl-2-azetidinone derivatives in good to excellent yield. The applications in the synthesis of carbapenem skeletons are discussed.

The experiments were carried out in THF with [3*R*(1′*R*,4*R*)]-(+)-4-acetoxy-3-[1′-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidin-one (**1**) and three equivalents of 3-bromoprop-1-yne (**2a**), in the presence of zinc powder. Initially, no reaction occurred at room temperature. When the temperature was elevated to 40 °C, the reaction was completed in 1.5 h, affording 4-propargyl-2-azetidinone (**3a**) in 65% yield. A high yield (81%) of **3a** was achieved at refluxing temperature;[11] however, a trace amount of the allenyl isomer **4a** was also formed (Fig. 1).[6a]

To our surprise, 4-allenyl-2-azetidinone (**4b**)[6a] was obtained exclusively in 83% yield when **1** reacted with 1-bromobut-2-yne (**2b**) under optimized conditions. Thus, we further investigated the methodology with a series of propargyl bromides to demonstrate the scope and utility of this type of reaction. For the alkyl propargyl bromides with less bulky substituents at γ-position (Table 1, entries 3, 4 and 5), **4** was obtained in good

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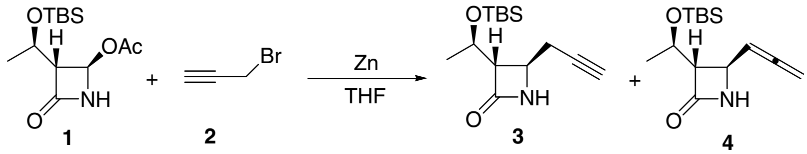
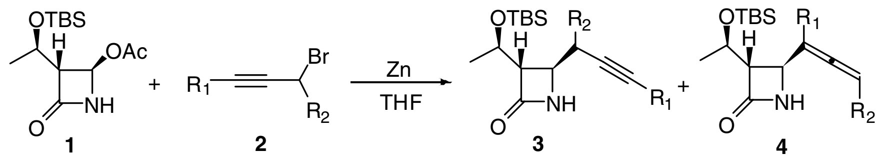


Figure 1. Introduction of propargyl group to the C4-position of 2-azetidinone.

Table 1. Reactions of 1 with propargyl bromides via zinc-mediated reaction



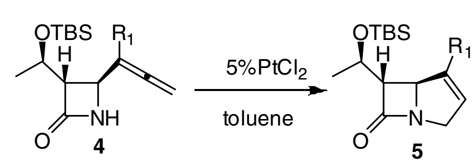
Entry	R_1	R_2	Time (min)	Yield[a] (%)	**3**:**4**[b]
1	H (**a**)	H	10	81	97:3
2	Me (**b**)	H	30	83	0:100
3	*n*-Bu (**c**)	H	30	90	9:91
4	$PhCH_2CH_2$ (**d**)	H	30	92	5:95
5	$CpCH_2$ (**e**)	H	30	89	0:100
6	Cyclopropyl (**f**)	H	30	80	58:42[c]
7	*t*-Bu (**g**)	H	30	92	50:50
8	Ph (**h**)	H	25	82	33:67
9	EtO_2C (**i**)	H	30	92	100:0[d]
10	$BnOCH_2$ (**j**)	H	30	81	61:39
11	$AcOCH_2$ (**k**)	H	30	70	67:33
12	Ph (**l**)	Me	20	97	100:0[e]
13	$BnOCH_2$ (**m**)	Me	10	89	100:0[f]
14	EtO_2C (**n**)	Me	10	100	100:0[d,g]

[a] Isolated yield.
[b] Separated by column chromatography, d.r. were determined by ^{1}H NMR.
[c] Some unseparated compounds was included in **3f**.
[d] 45 °C.
[e] d.r. (1α:1β) = 3:2.
[f] d.r. (1α:1β) = 2:1.
[g] d.r. (1α:1β) = 4:1.

yield with high selectivity. Otherwise, the 4-propargyl-2-azetidinone products increased significantly for propargyl bromide, bearing cyclopropyl, *t*-butyl or phenyl[10] groups at the γ-position (Table 1, entries 6, 7 and 8). The results implied that the steric hindrance might play an important role in achieving selectivity for this reaction. Likewise, the hetero atom (oxygen) at δ-position on the propargyl bromide had an adverse effect on the selectivity, **3j** and **3k** were obtained as the major products (Table 1, entries 10 and 11). 4-Propiolic ester derivative, having been converted to carbapenem,[12] was also successfully synthesized from the corresponding propargyl bromide in 92% yield (Table 1, entry 9), in contrast to the formation of allenyl product exclusively in 85% yield in an indium-mediated reaction.[10] For 3-bromo-but-1-yne derivatives, all the screened substrates (with phenyl,[10] BOM or ester substituted) gave the 4-propargyl-2-azetidinones in excellent yields and 1α-methyl isomers were the primary products (Table 1, entries 12, 13 and 14).[13]

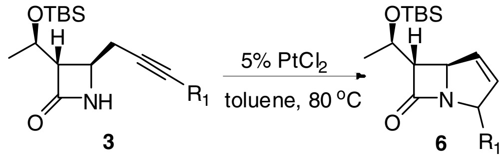
There are several notable reports on the construction of carbapenam skeletons with palladium,[4] silver[6] or gold[10] catalyzed intramolecular C–N bond forming reaction between amide N–H and allene. We found that treatment of 4-(1′-substituted allenyl)-2-azetidinone derivatives with 5 mol % $PtCl_2$ produced the corresponding bicyclic β-lactams in good yields.[14] Exposure

Table 2. $PtCl_2$ catalyzed cyclization of 4-allenyl-2-azetidinone derivatives



Entry	R_1	Temp (°C)	Time (h)	Yield[a] (%)
1	H (**a**)	40	25	69
2	Me (**b**)	40	24	89
3	*n*-Bu (**c**)	40	24	76
4	$PhCH_2CH_2$ (**d**)	40	48	74
5	$CpCH_2$ (**e**)	40	48	68
6	Cyclopropyl (**f**)	40	30	74
7	*t*-Bu (**g**)	40	48	78
8	Ph (**h**)	60	24	60
9	EtO_2C (**i**)	60	24	15 (64)
10	$BnOCH_2$ (**j**)	60	32	24 (49)
11	$AcOCH_2$ (**k**)	60	32	15 (57)

[a] Isolated yield; recovered starting materials in the bracket.



R_1	Yield	recovered S.M.
H (**a**)	13%	50%
Ph (**h**)	30%	42%
CO_2Et (**i**)	9%	55%

Figure 2. Cyclization of 4-propargyl-2-azetidinone derivatives promoted by $PtCl_2$.

of 4-allenyl-2-azetidinone **4a** to 5 mol% $PtCl_2$ in toluene produced the bicyclic β-lactam product **5a** in 69% yield (Table 2, entry 1), while 4-(1′-methylallenyl)-2-azetidinone **4b** gave the desired product **5b** in 89% yield (Table 2, entry 2).[6a] When the reaction was carried out with other azetidinones, the allene part bearing alkyl or aryl group[10] gave good yields of cyclization products (Table 2, entries 3–8). However, the 2-azetidinones allene with CO_2Et, $BnOCH_2$, and $AcOCH_2$ substituents gave poor yields and most of the starting materials were recovered (entries 9–11).

When 4-propargyl-2-azetidinone (**3a**) was treated with 5 mol% of $PtCl_2$ at 80 °C, the cyclization product **6a** with the unsaturated bond shifted to C1–C2 position was obtained in 13% yield (Fig. 2). The phenyl analog **3h** gave **6h** in slightly better yield under the same condition. Substrate **3i** also gave **6i** in 9% yield, which was close to the carbapenem. Unfortunately, screening various platinum compounds and additives did not improve the yield.

In summary, a convenient synthetic method for 4-allenyl-2-azetidinone and 4-propargyl-2-azetidinone derivatives has been established via Zn-mediated reactions. We have also demonstrated that $PtCl_2$ catalyzes intramolecular amidation of those products to afford carbapenem skeletons.

Acknowledgements

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11. Typical procedure for zinc-mediated reaction: A two-necked schlenk tube with a condenser was charged with **1** (100 mg) and zinc powder (102 mg, pre-treatment according to *Purification of Laboratory Chemicals*, fifth edition, Butterworth–Heinemann, 2003) under Ar. Then, THF (3 mL) and propargyl bromide (3 equiv) were added successively via a cannula at rt. The mixture was kept on a pre-heated oil bath and stirred under refluxed condition or 45 °C as indicated in Table 1 before it was allowed to cool to rt. After quenched by saturated NH_4Cl solution (4 mL), the mixture was extracted with EtOAc (4 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a residue that was further purified by column chromatography on silica (*EA:PE* = 1:4–1:6). Characterization data for representative compounds are shown as follows:
   Compound **4b**: FTIR (KBr) 3144, 3091, 2954, 2928, 2904, 2857, 1962, 1759, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (br s, 1H), 4.72–4.65 (m, 2H), 4.16–4.08 (m, 1H), 4.00 (d, $J = 2.1$ Hz, 1H), 2.89–2.85 (m, 1H) 1.64 (dd, J=3.0, 3.3 Hz, 3H), 1.13 (d, $J = 6.3$ Hz, 6H), −0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 168.4, 109.6, 98.3, 76.2, 65.1, 64.2, 51.3, 25.6, 22.5, 17.4, 14.5, −4.5, −5.1; HRMS (MALDI) calcd for $C_{15}H_{27}NO_2SiNa^+$ 304.1703, found 304.1716.
   Compound **3i**: FTIR (KBr) 3216, 2958, 2933, 2887, 2858, 2236, 1756, 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (br s, 1H), 4.22 (q, $J = 6.6$ Hz, 3H), 3.95–3.89 (m, 1H), 2.94–2.90 (m, 1H), 2.71–2.66 (m, 2H), 1.30 (t, $J = 6.6$ Hz, 3H), 1.22 (d, $J = 6.6$ Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 153.1, 83.8, 74.9, 64.7, 64.1, 61.9, 47.8, 25.5, 24.7, 22.4, 17.7, 13.8, −4.4, −5.2; HRMS (MALDI) calcd for $C_{17}H_{29}NO_4SiNa^+$ 362.1758, found 362.1766.
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13. The 1α, 1β-isomers of **3m**, **3n** were unseparated by column chromatography or recrystallization and the configuration of 1-methyl was assigned as the following methods: (a) comparing the ^1H NMR spectrograms of **3l** and sonogashira coupling product of iodobenzene and (3*S*,4*R*)-4-((*S*)-but-3-yn-2-yl)-3-((*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl)azetidin-2-one (**7**) prepared according to Ref. 7; (b) deprotecting the Bn group of **3m** with DDQ to the known free OH compound (Ref. 4b); (c) the pure 1β-isomer of **3n** was prepared from **7** by protecting NH with TBS, treating

with ethyl chloroformate after lithiation with *n*-BuLi, and deprotecting the TBS group.

14. Typical procedure for cyclization of 4-allenyl-2-azetidinones: Under N_2, **3**, $PtCl_2$ and toluene were added to the tube successively, the mixture was stirred for 20 h at appropriate temperature. The mixture was concentrated in vacuo and purified by flash column chromatography. Characterization data for representative compounds are shown as follows:

Compound **5b**: FTIR (KBr) 3056, 2975, 2930, 2859, 1772, 1642 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (s, 1H), 4.31–4.23 (m, 1H), 4.19–4.13 (m, 2H), 3.55–3.45 (m, 1H), 2.87 (dd, $J = 2.4$, 6.0 Hz, 1H), 1.78 (s, 3H), 1.22 (d, $J = 6.0$ Hz, 3H), 0.87 (s, 9H), 0.06(s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.7, 138.8, 125.8, 65.8, 65.5, 63.4, 53.1, 25.5, 22.5, 17.7, 12.7, −4.5, −5.1; HRMS(ESI) calcd for $C_{15}H_{27}NO_2Si$ 281.1811, found 281.1815.