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Cu-OMS-2-catalyzed decarboxylation–acetoxylation of (3*R*,4*R*)-4-acid-3-[(*R*)-1-((*t*-butyl-dimethylsilyl)oxy)-ethyl]-1-methoxyphenyl-2-azetidinone with $NaBrO_3$/NaOAc

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Abstract (3*R*,4*R*)-4-Acetoxy-3-[(*R*)-1((*t*-butyldimethylsilyl)oxy)-ethyl]-1-methoxy phenyl-2-azetidinone (an important precursor for the synthesis of carbapenem antibiotics) was synthesized under mild and green conditions catalyzed by Cu-OMS-2. Normal to excellent isolated yields were obtained under given conditions.

Keywords Azetidinone · Decarboxylation · Acetoxylation · Cu-OMS-2

Introduction

(3*R*,4*R*)-4-Acetoxy-3-[(*R*)-1((*t*-butyldimethylsilyl)oxy)-ethyl]-2-azetidinone (4AA) is the most convenient precursor to the carbapenem antibiotics, and a variety of syntheses of this compound have been performed. Currently the key factor restricting the synthesis of 4AA is formation of the acetoxy derivative of azetidinone—poisonous or expensive metals, for example lead [1–4], mercury [5], and ruthenium [6, 7] have been used as catalysts in industrial production. Therefore, it is a challenge to find an environmental and inexpensive catalyst for synthesis of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1((*t*-butyldimethylsilyl)oxy)-ethyl]-1-methoxyphenyl-2-azetidinone (**1**). However, there are few reports on this important process. In 2004, Laurent discovered the

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acetic acid–sodium acetate system, and the yield was 68 %, but the reaction time was too long (17 h) [8].

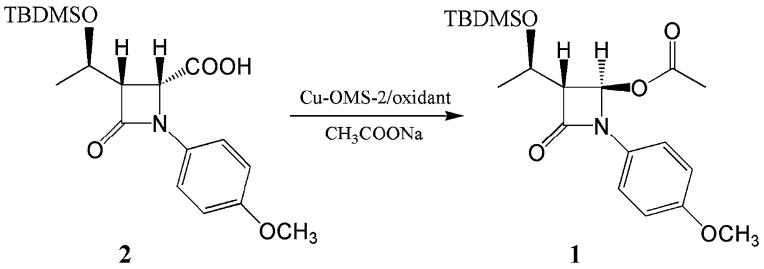
OMS-2 microporous molecular sieves have been used as catalysts of oxidative reactions, and Mn is a very effective catalyst for oxidative decarboxylation of acids [9]. Cu is an effective catalyst of oxidative acetoxylation of C–H bonds [10, 11]. We therefore supposed OMS-2 doped with copper could catalyze the reaction effectively (Scheme 1).

Results and discussion

XRD results (Fig. 1) showed OMS-2 microporous molecular sieves were essentially the same as that synthetic cryptomelane (Cryptomelane, KMn_8O_{16}) [12, 13]. The results showed that the synthetic samples contained typical manganese oxide octahedra. The two diffraction peaks at 2θ of approximately 39.5° and 72.64° arise as a result of diffraction by the CuO [14, 15]. This demonstrates that the copper has been successfully introduced into the OMS-2, and the pore structure of OMS-2 was not destroyed during the reaction processes. The copper content (analyzed by ICP) of synthesized samples was 0.08, 1.85, 4.15, and 4.98 % (wt%).

To begin our study, the effect of different conditions on the reaction of (3*R*,4*R*)-4-acid-3-[(*R*)-1((*t*-butyldimethylsilyl)oxy)-ethyl]-1-methoxyphenyl-2-azetidinone (**2**) with NaOAc was examined using 4.15 % Cu-OMS-2 as catalyst (Table 1). The results suggested that the oxidant had a dramatic effect on the reaction. Among the oxidants tested, only 13 % **1** was obtained by use of H_2O_2 (Table 1, entry 1). The yield was improved when O_2 or $(NH_4)_2S_2O_8$ was used in the reaction (Table 1, entries 2, 3). The reaction afforded **1** in 82 % yield in the presence of $NaBrO_3$ (Table 1, entry 4). Further study revealed that the catalyst had a dramatic effect on the reaction and 4.15 % Cu-OMS-2 was the best (Table 1, entries 4–7). Replacing acetic acid with other solvents, for example toluene, dichloromethane, and acetic ether significantly reduced the yields (Table 1, entries 8–10).

On the basis of these considerations, the effect of different quantities of Cu in the catalyst was studied (Fig. 2). This showed that the yield was only 64 % for 0.08 % Cu-OMS-2 but that when the quantity of Cu reached 1.85 %, the yield rose to 72 %. When the quantity of Cu reached 4.15 %, 82 % isolated yield was obtained. The



Scheme 1 Decarboxylation–acetoxylation of azetidinone

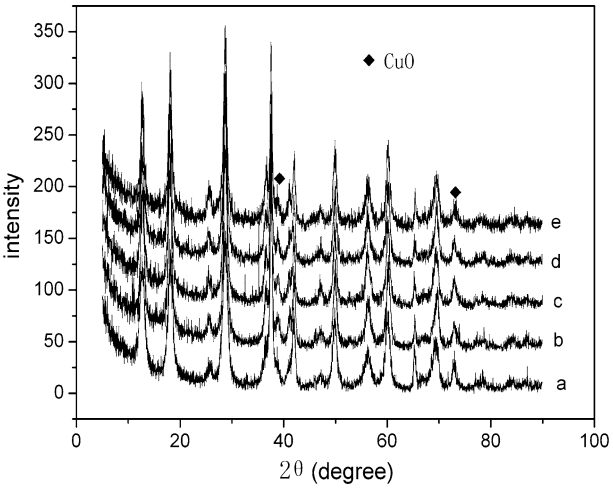


Fig. 1 XRD of Cu-OMS-2. (*a*) OMS-2; (*b*) 0.08 % Cu-OMS-2; (*c*) 1.85 % Cu-OMS-2; (*d*) 4.15 % Cu-OMS-2; (*e*) 4.98 % Cu-OMS-2

Table 1 Effects of catalyst and oxidant on reaction yield

Entry	Catalyst	Oxidant	Solvent	Isolated yield/%
1	4.15 % Cu-OMS-2	H_2O_2	Acetic acid	13
2	4.15 % Cu-OMS-2	$(NH_4)_2S_2O_8$	Acetic acid	47
3	4.15 % Cu-OMS-2	O_2	Acetic acid	54
4	4.15 % Cu-OMS-2	$NaBrO_3$	Acetic acid	82
5	–	$NaBrO_3$	Acetic acid	<10
6	$Cu(OAc)_2$	$NaBrO_3$	Acetic acid	45
7	OMS-2	$NaBrO_3$	Acetic acid	55
8	4.15 % Cu-OMS-2	$NaBrO_3$	Toluene	<5
9	4.15 % Cu-OMS-2	$NaBrO_3$	Dichloromethane	<5
10	4.15 % Cu-OMS-2	$NaBrO_3$	Acetic ether	<5

results showed that as the quantity of Cu was increased the yield also was improved. Use of an excessive quantity of Cu (4.98 %) reduced the yield, however.

From Fig. 3 we can see that the temperature has a great effect on the reaction. When the temperature was 45 °C, the reaction time was longer and the yield was only 53 %. When the temperature was 65 °C, the yield was 82 %. Only 67 % yield was obtained when the temperature was increased to 75 °C.

More experiments were conducted to gain preliminary insight into the reaction mechanism. A working mechanism was proposed, as outlined in Scheme 2. When copper was used, reaction of Cu with (3*R*,4*R*)-4-acid-3-[(*R*)-1((*t*-butyldimethylsilyl)oxy)-ethyl]-1-methoxyphenyl-2-azetidinone formed the copper(II) carboxylate. This copper(II) salt will quickly react with bromine to form the intermediate **4**, radical decarboxylation of which forms the radical **5**. **5** loses electrons to form

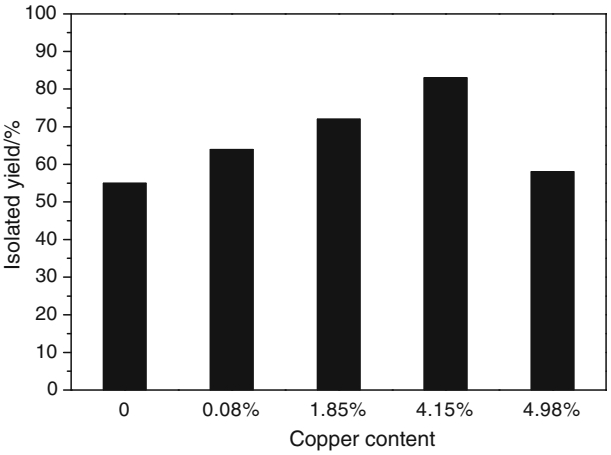


Fig. 2 Effect of copper content on reaction yield

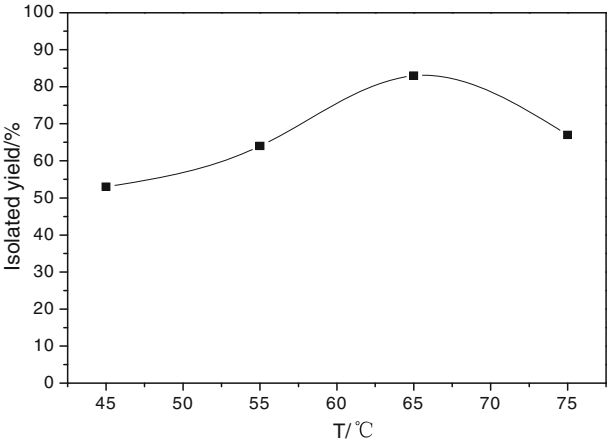
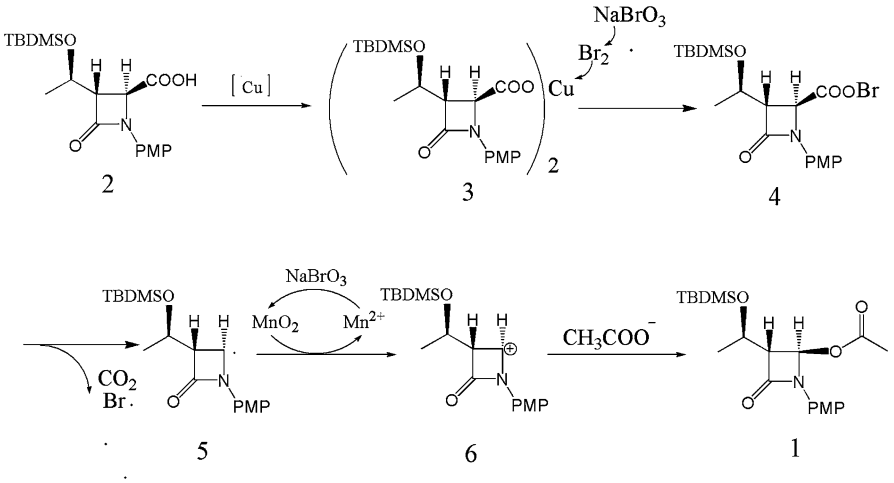


Fig. 3 Effect of temperature on reaction yield

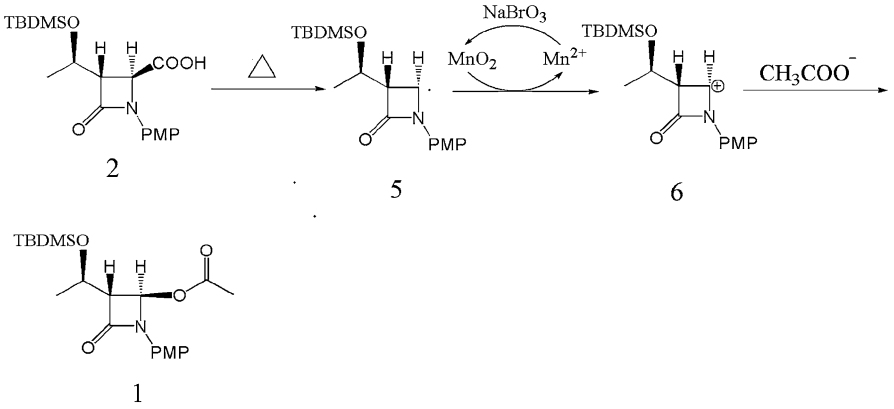
positive ions, which will quickly recombine to form the product **1**. The mechanism proposed in the absence of copper is outlined in Scheme 3. When heated, **2** will be decarboxylated to form the radical **5**, but the process needs higher activation energy than when copper participates in the reaction; this will cause a large decrease in yield (Table 1, entry 7). Because this is a complex reaction, we only give a possible reaction mechanism; detailed studies are in progress.

Conclusion

In summary, a series of well-structured Cu-OMS-2 mesoporous samples were synthesized. When the samples were used as catalysts for the decarboxylation–acetoxylation



Scheme 2 Mechanism 1



Scheme 3 Mechanism 2

of (3*R*,4*R*)-4-acid-3-[(*R*)-1-((*t*-butyldimethylsilyl)oxy)-ethyl]-1-methoxyphenyl-2-azetidinone, an important reaction in the pharmaceutical industry, the synthetic samples had good catalytic activity and an excellent isolated yield was obtained. Detailed studies are in progress.

Experimental

Preparation of Cu-OMS-2 materials

$Cu(OAc)_2$ (0.2, 0.5, 1.0, or 2.0 g) was dissolved in 50 ml demineralized water then 5 g OMS-2 was added. The mixture was stirred overnight at room temperature. The

dark brown solid product was isolated by filtration and washed and dried in an air oven at 80 °C for 12 h.

Traditional procedure for synthesis of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1((*t*-butyldimethylsilyl)oxy)-ethyl]-1-methoxyphenyl-2-azetidinone (1)

The reaction was conducted with **2** (0.026 mol), $NaBrO_3$ (2 equiv), 4.15 % Cu-OMS-2 (1.15 g), and NaOAc (1.5 equiv) in 60 ml acetic acid under air at 65 °C for 3 h. After removal of the solvent in vacuo, the residual products were dissolved by ethyl acetate (100 ml). The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved by methanol (100 ml), additional water (100 ml) was added dropwise over 20 min, and the mixture was stirred for 0.5 h at 5 °C. The resulting precipitate was isolated by filtration and dried in vacuo to give **1** as colorless crystals (8.5 g, 82 %). mp 76–77 °C; ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.75 (s, 9H, *t*-Bu), 1.34 (d, $J = 6.0$ Hz, 3H, CH_3), 2.10 (s, 3H, $COCH_3$), 3.18 (d, $J = 3$ Hz, 1H, CH_3), 3.76 (s, 3H, OCH_3), 4.34 (m, 1H, CH), 6.27 (s, 1H, CH_3), 6.72 (d, $J =$ 10.4 Hz, 2H, ArH), 7.24 (d, $J = 10.4$ Hz, 2 H, ArH). ^{13}C NMR: 169.84, 163.55, 156.26, 129.46, 118.33, 114.24, 76.64, 65.33, 64.14, 55.42, 25.62, 22.35, 21.14, 17.79, −4.18, −5.05.

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