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Ultrasound-induced catalytic transfer hydrogenolysis of β-lactams: Facile synthesis of 2-hydroxy aromatic amide derivatives

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Ammonium format and 10% Pd/C-induced ultrasound-mediated hydrogenation was performed on β-lactams to produce α-hydroxy amide derivatives. This reaction depends on the substitution on N^1-C^4 position of β-lactam ring. A most probable mechanism of this reaction is advanced.

Keywords: Ultrasound, hydrogenolysis, β-lactam, ammonium formate, hydroxy amide.

Introduction

The β-lactam ring are integral structural motif present in diverse antibiotics and are well known chemotherapeutic drugs used for the treatment of variety of infectious disease[1–5]. Albiet potential chemotherapeutic application they also serve as an important synthetic building blocks in the synthesis of medicinally privileged molecules[6–9].

In continuation of our efforts towards the development of newer synthetic strategy for the β-lactam synthesis and their medicinal application, we report here our unprecedented results based on hydrogenation reaction of β-lactam compounds.

Hydrogenation and hydrogenolysis with metal catalysts are extremely fundamental reactions in chemistry[10,11]. In general, this reaction is conducted with metal catalyst (for example, palladium) and hydrogen gas under pressure[12,13]. To avoid hydrogen gas, scientists have used different other reagents to overcome their flammability and danger during chemical reaction. Some of these methods have become attractive. These procedures include formate salts[14], Raney nickel[15], hydrazine[16], cyclohexadiene[17] and cyclohexene[18] as the source of hydrogen gas.

Ultrasound-induced hydrogenolysis of β-lactams with C-4 aryl group to hydroxy amide derivatives is achieved by catalytic transfer hydrogenation in excellent to good yield. This method is rapid and produced products within a few minutes under the condition stated. However, sterically congested β-lactams derived from polycyclic aromatic iminedo not undergo N^1-C^4 bond cleavage under this condition. It is well documented in literature that cleavage of N^1-CO bond in β-lactam is facile and could be easily achieved by the attack of nucleophiles viz. H_2O.

There are other possibilities of β-lactam ring cleavage reactions. The most probable is N^1-C^4 which could open the new possibility for the synthesis valuable class of leading compounds like β-amino acid, α-hydroxy acid, polyamides and polyamino-alcohol (Fig. 1)[19–22].

Results and discussion

The main limitation of the catalytic hydrogenation and hydrogenolysis is the use of hydrogen gas in this process.

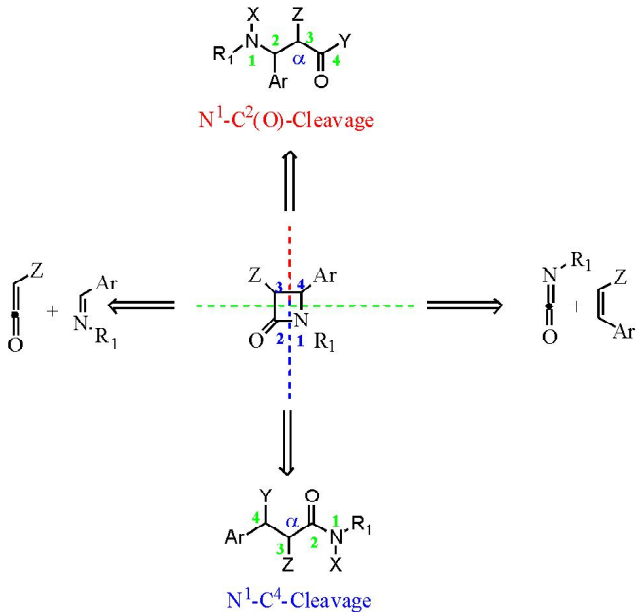
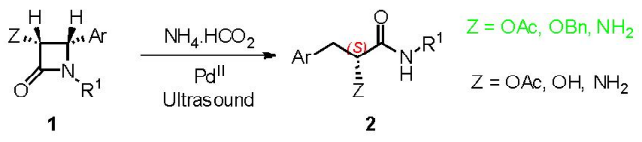


Fig. 1. Possible bond cleavage in β-lactam ring.

Hydrogen gas is flammable in the presence of metals. It is also necessary to remove excess hydrogen gas from the reaction mixture by a vacuum pump to avoid explosion or fire. In catalytic transfer hydrogenation procedure, a hydrogen gas donor is used at different temperature. In general, alternative method is milder, less time consuming and easy to handle in comparison to conventional catalytic reduction method.

We have been engaged in the synthesis and biological evaluation of β-lactams for almost 30 years. On this basis, we have prepared numerous diverse β-lactams. It was found that monocyclic β-lactams with aromatic groups at nitrogen and C-4 carbon undergo ring cleavage in the presence of catalytic hydrogenation and transfer hydrogenation method. This reaction produced open chain aromatic amides with diverse substitution. Ultrasound-mediated reaction proceed smoothly at 40°C temperature and the amides were obtained within 10 min (Scheme 1).



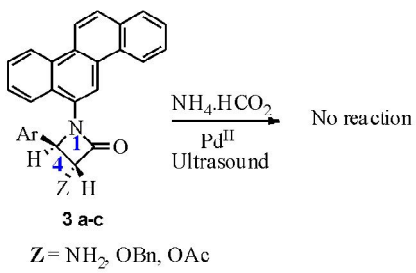
Scheme 1. Synthesis of (+/–)-α-hydroxy/amino-N-arylamide by catalytic hydrogenation under ultrasound condition.

Table 1. Synthesis of (+/–) *racemic* α-hydroxy/amino-N-arylamides by palladium catalyzed catalytic hydrogenation under ultrasound irradiation[a]

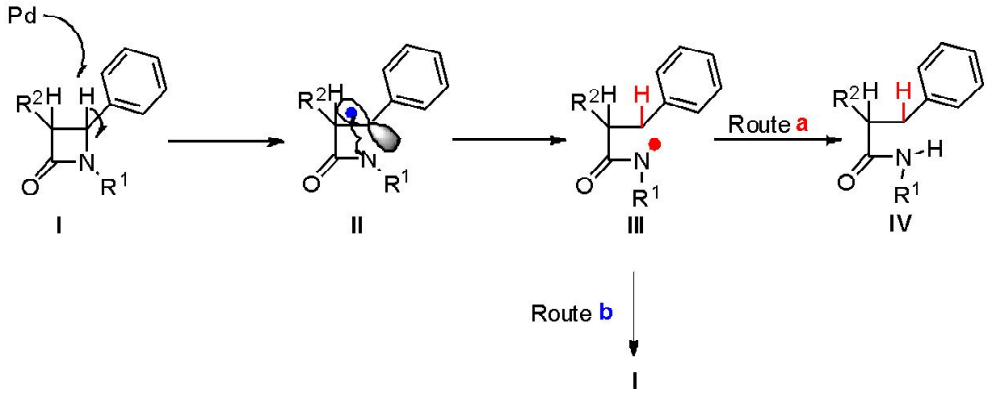
Entry	Ar	R^1	Z	Condition(s) (°C, min)	Yield[b] (%)
1	C_6H_5	C_6H_5	NH_2	40, 5	70
2	C_6H_5	C_6H_5	OH	40, 10	80
3	C_6H_5	C_6H_5	OAc	40, 7	90
4	C_6H_5	4-MeO-C_6H_4	NH_2	40, 5	85
5	C_6H_5	4-MeO-C_6H_4	OH	40, 10	80
6	C_6H_5	4-MeO-C_6H_4	OAc	40, 7	90
7	4-MeO-C_6H_4	C_6H_5	NH_2	40, 8	85
8	4-MeO-C_6H_4	C_6H_5	OH	40, 10	75
9	4-MeO-C_6H_4	C_6H_5	OAc	40, 6	80
10	4-F-C_6H_4	C_6H_5	NH_2	40, 8	85
11	4-F-C_6H_4	C_6H_5	OH	40, 10	80
12	4-F-C_6H_4	C_6H_5	OAc	40, 6	90
13	4-Me-C_6H_4	C_6H_5	NH_2	40, 7	80
14	4-Me-C_6H_4	C_6H_5	OH	40, 10	85
15	4-Me-C_6H_4	C_6H_5	OAc	40, 6	90

[a]All reaction was carried out with 1 mmol of beta-lactam, 3 equivalent of ammonium formate and 20–50 mg of palladium charcoal in 2–3 mL of ethanol under ultrasound-assisted reaction. [b]Isolated yield after purification.

To diversify the method and to correlate the anticancer activity of amides derived from polyaromatic compounds, an attempt was made to cleave the N^1-C^4 bond of *trans* N-chrysenyl-3-acetoxy-4-phenyl-2-azetidinone **3c** and *trans* N-chrysenyl-3-phenoxy-4-phenyl-2-azetidinone **3b** following ultrasound-mediated method. Interestingly, no N1-C4 bond cleavage was occurred in **3a** or **3b**. The starting materials were recovered unchanged. Microwave irradiation method was also performed with **3c** and **3b** using 10% Pd/C and ammonium formate at 80 degree. But no open chain amides were formed (Scheme 2).



Scheme 2. Attempt to cleavage of N^1-C^4 bond in polyaromatic β-lactams..



Scheme 3

The unusual behavior of polycyclic β-lactams derived from corresponding imine has greater bond energy associated with N^1-C^4 bond of polyaromatic system. This is hypothesized that the bulkier aromatic group cause heavy stearic hindrance which impedes the approach of the hydrogen radical to cleave the N^1-C^4 bond.

Mechanistically, these results can be explained through the formation of radical produced by the attack of palladium metal. Palladium assists a homolytic cleavage of benzylic proton of beta-lactam ring (**I**). A second homolysis of C-N bond produces a nitrogen radical (**II**). Intermediate **III** adopts the route **I** to give amide (**IV**) in good yield when monocyclic aromatic rings are present in N- of the ring. The driving force is due to the stabilization of nitrogen radical through back donation of the electron loan pair of carbonyl oxygen to the empty *p*-orbital. This produces a stable radical. Polyaromatic ring at N atom causes greater steric hindrance and as a result stabilization of radical intermediate is greatly hindered. In addition, it appears polyconjugated system prefers pi-staking rather than stabilizing the nitrogen radical and thus, the system reverts to the starting compound (Scheme 3).

Conclusions

Preparation of 2-hydroxy derivatives N-aryl amides is achieved through ultrasound-mediated method. This reaction is depended on the steric hindrance of the group present at the nitrogen of the beta-lactams. It is important to note that functionalization of the C-position of an aromatic amide is difficult through a direct approach. Therefore, considering the importance of the products described herein and the simplicity of the method, we believe this method may find wide application in chemical science.

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References

1. R. C. Moellering, G. M. Eliopoulos and D. E. Sentochnik, *J. Antimicrob. Chemother.*, 1989, **24**, 1. https://doi.org/10.1093/jac/24.suppl_A.1.
2. M. Paul, A. Lador, S. Grozinsky-Glasberg and L. Leibovici, *Cochrane Database Syst. Rev.*, 2014, **1**. https://doi.org/10.1002/14651858.CD003344.pub3.
3. J. A. Roberts, M. Ulldemolins, M. S. Roberts, B. McWhinney, J. Ungerer, D. L. Paterson and J. Lipman, *Int. J. Antimicrob. Agents,* 2010, **36(4)**, 332. https://doi.org/10.1016/j.ijantimicag.2010.06.008.
4. K. B. Holten and E. M. Onusko, *Am. Fam. Physician,* 2000, **62(3)**.
5. F. Baquero, *Microb. Drug Resist.*, 2009, **1(2)**, 115. https://doi.org/10.1089/mdr.1995.1.115.
6. B. Alcaide and P. Almendros, *Chem. Soc. Rev.*, 2001, **30(4)**, 226. https://doi.org/10.1039/b007908l.
7. C. Palomo, J. Aizpurua, I. Ganboa and M. Oiarbide, *Curr. Med. Chem.*, 2012, **11(14)**, 1837. https://doi.org/10.2174/0929867043364900.
8. B. Alcaide, P. Almendros and C. Aragoncillo, *Chem. Rev.*, 2007, **107(11)**, 4437. https://doi.org/10.1021/cr0307300.
9. B. Alcaide and P. Almendros, *Curr. Med. Chem.*, 2012, **11(14)**, 1921. https://doi.org/10.2174/0929867043364856.
10. R. A. W. Johnstone, A. H. Wilby and I. D. Entwistle, *Chem. Rev.*, 1985, **85(2)**, 129. https://doi.org/10.1021/cr00066a003.
11. R. A. Sheldon and H. Van Bekkum, "Fine Chemicals through Heterogeneous Catalysis", John Wiley & Sons, 2008. https://doi.org/10.1002/9783527612963.

12. H. U. Blaser, A. Indolese, A. Schnyder, H. Steiner and M. Studer, *J. Mol. Catal. A: Chem.*, 2001, **173(1-2)**, 3. https://doi.org/10.1016/S1381-1169(01)00143-1.
13. K. Sato, N. Oka, S. Fujita, F. Matsumura and T. Wada, *J. Org. Chem.*, 2010, **54(20)**, 4738. https://doi.org/10.1021/jo902725g.
14. Z. Paryzek, H. Koenig and B. Tabaczka, *Synthesis (Stuttg)*, 2003, **2003(13)**, 2023. https://doi.org/10.1055/s-2003-41024.
15. R. Raja, V. B. Golovko, J. M. Thomas, A. Berenguer-Murcia, W. Zhou, S. Xie and B. F. G. Johnson, *Chem. Commun.*, 2005, **15**, 2026. https://doi.org/10.1039/b418273a.
16. Z. Zhang, I. R. Ollmann, X. S. Ye, R. Wischnat, T. Baasov and C. H. Wong, *J. Am. Chem. Soc.*, 1999, **121(4)**, 734. https://doi.org/10.1021/ja982232s.
17. A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki and J. Meienhofer, *J. Org. Chem.*, 1978, **43(21)**, 4194. https://doi.org/10.1021/jo00415a045.
18. D. Geburtig, P. Preuster, A. Bösmann, K. Müller and P. Wasserscheid, *Int. J. Hydrogen Energy,* 2016, **41(2)**, 1010. https://doi.org/10.1016/j.ijhydene.2015.10.013.
19. I. Ojima, *Acc. Chem. Res.*, 1995, **28(9)**, 383. https://doi.org/10.1021/ar00057a004.
20. A. Kamath and I. Ojima, *Tetrahedron,* 2012, **68(52)**, 10640. https://doi.org/10.1016/j.tet.2012.07.090.
21. I. Ojima and F. Delaloge, *Chem. Soc. Rev.*, 1997, **26(5)**, 377. https://doi.org/10.1039/CS9972600377.
22. B. Alcaide and P. Almendros, *Synlett.,* 2002, **2002(3)**, 0381. https://doi.org/10.1055/s-2002-20448.