proceedings

MDPI

Proceedings

Industrial Method for Preparing 3-Chloromethyl Oxacephem Antibiotic Nucleus

Dong-Jun Fu

New Drug Research & Development Center, School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, China; zzufdj@sina.com

Abstract: 3-Chloromethyl oxacephem as a 5-oxa-1-azabicyclo[4.2.0]oct-2-en-8-one heterocycle displayed the potent antibacterial activity against both Gram-positive and Gram-negative bacteria. Importantly, it can be used as a starting material to synthesize Latamoxef and Flomoxef as famous antibiotic drugs. However, the industrial route of 3-chloromethyl oxacephem is trival and low yielding. Therefore, discovery a simple and productive synthetic method is very necessary. The inexpensive 6-Aminopenicillanic acid was used to obtain the 3-chloromethyl oxacephem in our group.

Keywords: 3-chloromethyl oxacephem; antibacterial activity; Latamoxef; Flomoxef.

1. Introduction

Antibacterial substances are of great importance and necessity in treating infectious diseases caused by pathogenic bacteria[1]. Due to its unique antimicrobial activity and novel structure among the synthetic antibiotics, 1-oxacephem core structure as an important pharmaceutical scaffold has attracted immense interest for medicinal chemists[2-4]. A variety of synthetic compounds prepared from 1-oxacephem intermediate, including prominent antibiotics such as Flomoxef and Moxalactam (Figure 1), have a broad spectrum of activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria[5].

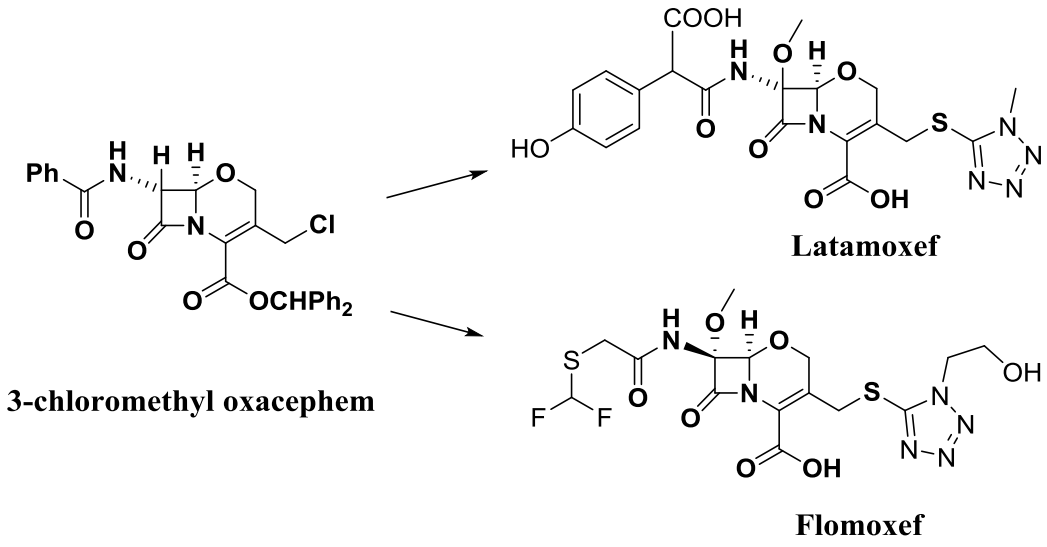
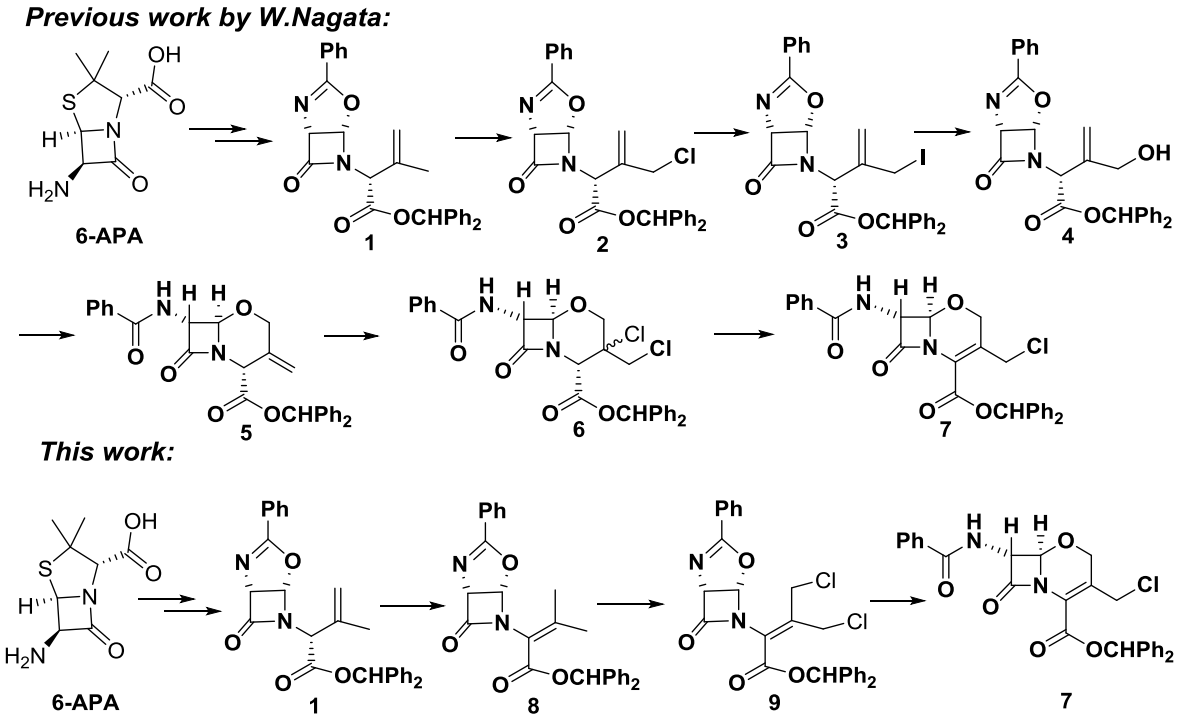


Figure 1. Synthetic 1-oxacephem antibiotics

Recently, an large-scale feasible route to synthesize 1-oxacephem starting from commercially available 6-aminopenicilanic acid (6-APA) (Scheme 1) was reported by W. Nagata in Shionogi company[6]. In this sophisticated method designed to retain all the carbon atoms, preparing epioxazolinoazetidinones having an unconjugated ester moiety at the β-lactam nitrogen was a

breakthrough. Although widely used, the existing protocol for the synthesis of 1-oxacephem was tedious, labor intensive. Therefore, the possibility of synthesizing 1-oxacephem from a conjugated ester as the key intermediate in a simple method, was investigated (Scheme 1).



Scheme 1. Synthesis of 1-oxacephem

2. Methods

All reagents and solvents used were of analytical grade purchased from commercial sources. Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel (Qingdao Haiyang Chemical Co., G60F-254) and visualized by UV light (254 nm). The products were purified by column chromatography over silica gel (Qingdao Haiyang Chemical Co., 300 mesh). Melting points were determined on a Beijing Keyi XT4A apparatus and are uncorrected. All NMR spectra were recorded with a Bruker DPX 400 MHz spectrometer with TMS as internal standard. Chemical shifts are given as δ ppm values relative to TMS. Mass spectra (MS) were recorded on Esquire3000 mass spectrometer by electrospray ionization (ESI).

3. Results

Compound(7): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83(d, J=7.9 Hz, 2H), 7.55~7.27(m, 13H),7.04 (d,J=7.2,1H) 6.95 (s, 1H), 5.06(s, 1H), 5.00(d, J = 7.2Hz, 2H), 4.63(dd, J=18.08, 2H), 4.44(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.53, 162.54, 159.63, 139.40, 139.11, 132.64, 132.25, 128.68, 128.64, 128.51, 128.30, 128.11, 127.52, 127.39, 126.95, 124.48, 82.87, 79.95, 69.30, 66.18, 64.03, 38.96. HRMS (ESI): m/z calcd for $C_{28}H_{23}ClN_2NaO_5$ $(M+Na)^+$, 525.1193; found, 525.1196.

4. Conclusions

In summary, we developed a novel and concise approach for the synthesis of 1-oxacephem scaffold **(7)**. Compared with the six steps method by Shionogi company from epi-oxazoline **(1)**, new strategy prepared the target compound **(7)** in a three-step process from the same starting material **(1)**. The overall yield is 43.75%. Furthermore, it can avoid to using virulent chlorine and heavy metal agents, which is so friendly to our environment.

Acknowledgments: Dong-Jun Fu is grateful for the financial support from the Outstanding PhD Training Program of Zhengzhou University and the China Scholarship Council (CSC).

Author Contributions: D-J. Fu. Designed and performed the experiments.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Payne, D.J..; Gwynn, M.N..; Holmes, D.J..; Pompliano, D.L. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nature Reviews Drug Discovery*. **2007**, *6*, 29.
2. Aoyama, Y..; Uenaka, M..; Konoike, T..; Iso, Y..; Nishitani, Y..; Kanda, A..; Naya, N..; Nakajima, M. 1-Oxacephem-based human chymase inhibitors: discovery of stable inhibitors in human plasma. *Bioorganic & Medicinal Chemistry Letters*. **2000**, *10*, 2403.
3. Fu.; Dongjun.; Liu.; Yingchao.; Li.; Feng.; Zhang.; En.; Liu.; Hongmin. Recent Advances in Asymmetric Synthesis of Oxacephems. *Chinese Journal of Organic Chemistry*. **2015**, *35*, 947.
4. Fu, D.-J..; Fu, L..; Liu, Y.-C..; Wang, J.-W..; Wang, Y.-Q..; Han, B.-K..; Li, X.-R..; Zhang, C..; Li, F..; Song, J..; Zhao, B..; Mao, R.-W..; Zhao, R.-H..; Zhang, S.-Y..; Zhang, L..; Zhang, Y.-B..; Liu, H.-M. Structure-Activity Relationship Studies of β-Lactam-azide Analogues as Orally Active Antitumor Agents Targeting the Tubulin Colchicine Site. *Scientific Reports*. **2017**, *7*, 12788.
5. Jost, G..; Bloemberg, G.V..; Hombach, M. Improved sensitivity for methicillin-resistance detection in coagulase-negative staphylococci by moxalactam antibiotic disks or a cefoxitin investigation zone. *Journal of Medical Microbiology*. **2016**, *65*,
6. Otsuka, H..; Nagata, W..; Yoshioka, M..; Narisada, M..; Yoshida, T..; Harada, Y..; Yamada, H. Discovery and development of moxalactam (6059-S): The chemistry and biology of 1-oxacephems. *Medicinal Research Reviews*. **1981**, *1*, 217.