头孢托仑酯合成路线图解

陈林，石克金，李江红

（中国医药集团 四川抗菌素工业研究所，成都 610052）

Graphical Synthetic Routes of Cefditoren Pivoxil

CHEN Lin, SHI Ke-jin, Li Jiang-hong

(Sichuan Industrial Institute of Antibiotics, China National Pharmaceutical Group Corporation, Chengdu 610052, China)

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头孢托仑酯(Cefditoren Pivoxil, **1**)1994年由日本明治制果公司开发，用于治疗革兰阳性菌及革兰阴性菌引起的感染,对多种细菌都显示出很强的抗菌效力。由于头孢托仑酯抗菌谱广,因而广泛应用于临床。本文对1的合成方法进行了归纳总结。

1　1的合成（见图1）

1.1 **21**与NaI、TPP(三苯基磷)搅拌反应，再加入NaOH水溶液处理。分离有机相，和**3**发生Wittig反应得**22**。苯酚溶解**22**，搅拌脱去2-位保护基对甲氧苄基，再用$NaHCO_3$水溶液提取，酸化后析出，即得**23**。**23**溶于DMF，加入K_2CO_3，再与特戊酸碘甲酯反应，得**24**。用PCl_5、吡啶、甲醇脱去**24**的7-位保护基苯乙酰基，得**25**。**25**与**36**[即 2-(2-三苯甲基氨基2-噻唑基)-2-甲氧亚胺乙酸]在吡啶和$POCl_3$的作用下缩合反应，柱层析分离得到**26**。**26**用CF_3COOH脱去三苯基甲基(Tri)得到1[1, 2, 4, 6, 9]。

1.2 **21**用PCl_5、吡啶、甲醇脱去7-位保护基苯乙酰基得**27**。**27**在DCC或吡啶和$POCl_3$的作用下与**36**进行酰化反应得到**29**。**29**与NaI、TPP搅拌反应，再加入NaOH水溶液处理，和**3**发生Wittig反应得**30**，**30**脱除保护基得**2**。**2**(或其钠盐、钾盐)与特戊酸碘甲酯进行酯化反应得**1**[1, 10, 11]。

1.3 **27**与NaI、TPP搅拌反应，再加入NaOH水溶液处理，和**3**发生Wittig反应得**28**(也可由**22**用PCl_5、吡啶、CH_3OH脱去苯乙酰基得到)，**28**与**36**发生缩合反应得**30**，再按1.2法得**1**[1、2]。

1.4 **28**用苯酚、苯甲醚脱去2-位对甲氧苄基得**20**，**20**与**37**(氨噻肟酸的苯并噻唑活性酯、苯并三唑活性酯、亚磷酸酯、嗯唑酯等)在碱化剂作用下缩合反应得**2**，再得1[1, 2, 8]。

1.5 **23**以PCl_5、吡啶、CH_3OH脱去苯乙酰基(或：**23**溶于$NaHCO_3$水溶液，用青霉素酰化酶Pen-G脱去苯乙酰基)得**20**，再按1.4法得**2**，得**1**[1, 7, 9]。

1.6 **34**直接[R=-$SO_3CN(CH_3)_2$]或在DCC(R=OH时)作用下与**20**反应得到**35**，**35**再与硫脲发生闭环反应合成噻唑环而得到**2**，得**1**[5, 7]。

1.7 **31**(即：头孢噻肟酸)用TMSC(三甲基氯硅烷)及HMDS(六甲基二硅胺)硅烷化，再用TMSI碘代得**32**。**32**与PPh_3、NaI、碱作用得叶立德**33**。**33**与**3**进行Wittig反应，并脱去保护基，得**2**，再得**1**[3]。

2　中间体3的合成（见图2）

2.1 丙酮和硫脲在碘的作用下，加热回流，闭环而得**4**。$POCl_3$/DMF作用于**4**在其5-位引入甲酰基得到**5**。浓硫酸作用于**5**，与$NaNO_2$进行重氮化反应，再用次磷酸钠处理，最终脱去氨基得到**3**[12]。

2.2 **6**在引发剂AIBN的作用下，与NBS发生选择性溴代反应得到**7**。**7**与$C_{16}H_{12}N_4$反应成盐得**8**，**8**加热水解得**3**[13]。

2.3 **9**用氢化铝锂还原(**10**用$NaBH_4/AlCl_3$还原)得**11**。**11**氧化(氧化剂MnO_2、KBr/TEMPO、氯铬酸吡啶盐等)得**3**[14-16, 22]。

2.4 维生素B1以$NaHSO_3$水解得**12**，**12**以CrO_3/H_2SO_4氧化裂解得**3**[17, 18]。

2.5 $SOCl_2$作用于**13**得酰氯**14**，再氢化还原得**3**[19]。

2.6 **15**在臭氧作用下，发生烯烃裂解反应而得**3**[20]。

2.7 溴素作用于**16**，得到**17**。乙二醇保护**17**的甲酰基

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作者简介：陈林，硕士，主要从事化学合成新药研究。

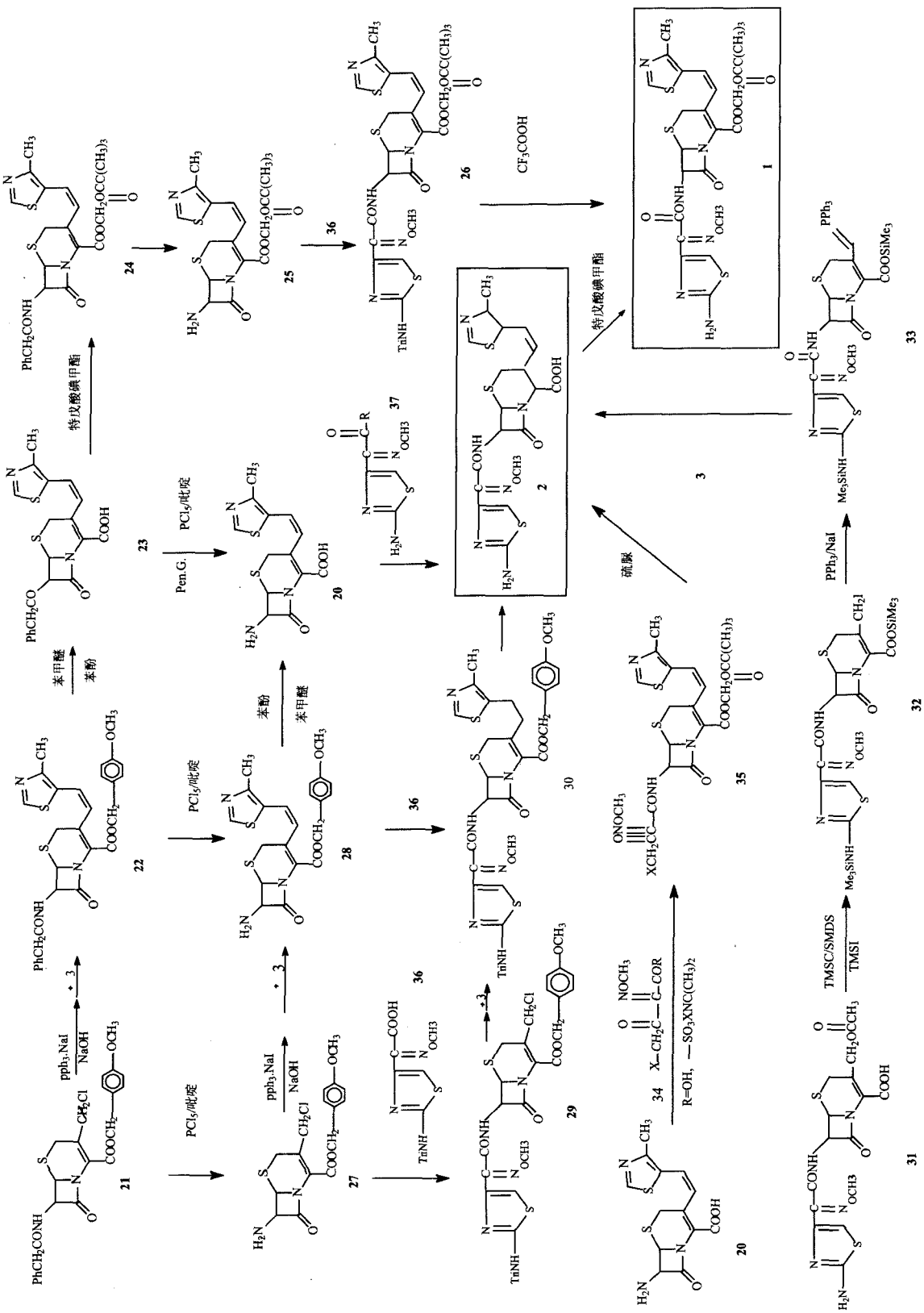

图 1 1 的合成路线图解

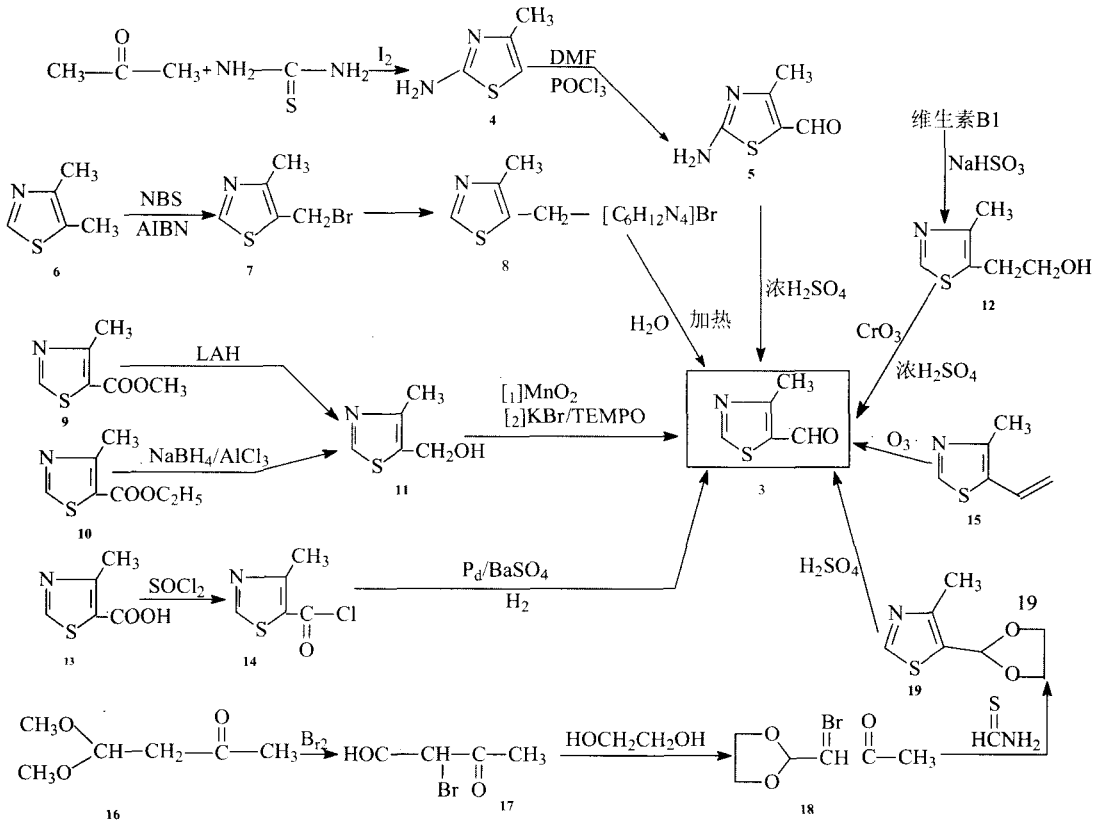

图 2　中间体3的合成路线图解

得缩醛**18**。**18**与硫代甲酰胺反应，闭环生成噻唑缩醛**19**。硫酸水解缩醛**19**得**3**[21]。

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