Tetrahedron Letters,Vol.23,No.21,pp 2187-2188,1982 0040-4039/82/212187-02$03.00/0
Printed in Great Britain 

# PENICILLIN-CEPHALOSPORIN CONVERSION III.
## A NOVEL ROUTE TO 3-CHLOROMETHYL- $\Delta^3$-CEPHEMS

Sigeru Torii,* Hideo Tanaka, Norio Saitoh, Takashi Siroi,
Michio Sasaoka, and Junzo Nokami†
Department of Industrial Chemistry, School of Engineering,
Okayama University, Okayama 700, Japan
†Okayama University of Science, Ridai, Okayama 700 Japan

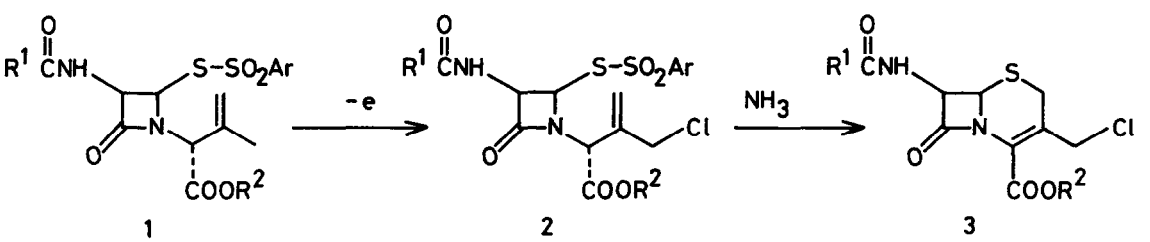
ABSTRACT: Synthesis of 3-chloromethyl-$\Delta^3$-cephems 3 from 4-arenesulfonylthioazetidin-2-ones 1, derived from penicillins G and V, has been achieved by the electrolytic ene-type chlorination of 1 in a $CHCl_3$-aqueous NaCl-$H_2SO_4$-(Pt electrodes) system and subsequent ring closure with $NH_3$ in DMF.

3-Chloromethyl-$\Delta^3$-cephems 3 are important precursors in the synthesis of 3'-substituted cephalosporin antibiotics.[1] They have been prepared from 3-acetoxymethyl cephalosporins by displacement of the acetoxy group with clorine atom.[2,3] Recent growing interest in the penicillin-cephalosporin conversion as an economical sense enable us to develop a straightforward synthetic route to 3 from azetidinones 1, prepared from natural penicillins.[4]

The conversion of 1 to 3 comprises the electrolytic ene-type chlorination[5] of 1 and the ring closure of 2 with base (Scheme 1). We found that the arenesulfonyl groups ($Ar-SO_2$) have a sufficient nature for both protecting the thiol groups at C(4)-position in electrolysis conditions (1 ⟶ 2) and playing the part of leaving groups in cyclization conditions (2 ⟶ 3). Some of our results are summarized in the Table.

A typical procedure is as follows (entry 1). A solution of 1a ($R^1$ = $PhCH_2$, $R^2$ = $CH_3$, Ar = p-$NO_2Ph$, 0.2 mmol) in $CHCl_3$ (5 ml) and aqueous NaCl (2 g/6 ml) containing $H_2SO_4$ (0.14 ml)

Scheme 1




1 2 3

Table.

| entry | $R^1$ | $R^2$ | Ar | yields, %[a] 1 → 2 | 2 → 3 |
|---|---|---|---|---|---|
| 1 | $PhCH_2$ | $CH_3$ | p-$NO_2Ph$ | 83 | 74 |
| 2 | $PhCH_2$ | $CH_3$ | Ph | 77 | 82 |
| 3 | $PhCH_2$ | $PhCH_2$ | p-$NO_2Ph$ | 91 | 86 |
| 4 | $PhCH_2$ | $PhCH_2$ | Ph | 84 | 78 |
| 5 | $PhCH_2$ | p-$NO_2PhCH_2$ | p-$NO_2Ph$ | 75 | 52 |
| 6 | $PhOCH_2$ | $PhCH_2$ | p-$NO_2Ph$ | 94 | 93 |

a) Isolated yields after column chromatography ($SiO_2$).

were charged in a cell fitted with two Pt foil electrodes (1.5 x 2 $cm^2$). Electrolysis was carried out under a constant current of 10 $mA/cm^2$ at 7-12 °C for 1.3 h (8 F/mol of electricity passed). The organic layer was separated and worked up in the usual manner, yielding 2a ($R^1$ = $PhCH_2$, $R^2$ = $CH_3$, Ar = p-$NO_2Ph$, 83%): IR ($CHCl_3$) 3400 (NH), 1780, 1745, 1673 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) δ 3.57 (s, 2H), 3.76 (s, 3H), 4.17 (bs, 2H), 4.90 (s, 1H), 5.05 (dd, 4.4, 7 Hz, 1H), 5.18 (s, 1H), 5.35 (s, 1H), 5.94 (d, 4.4 Hz, 1H), 6.50 (d, 7 Hz, 1H), 7.28 (s, 5H), 7.98 (d, 8 Hz, 2H), 8.37 (d, 8 Hz, 2H).

The ring closure of 2a (0.1 mmol) was accomplished by treatment with $NH_3$ (gas, 0.3 mmol) in DMF (0.5 ml) at -20 ~ -30 °C for 1 h, yielding 3a ($R^1$ = $PhCH_2$, $R^2$ = Me, 74%) without contamination of the $\Delta^2$-isomer. With regard to the cyclization with base, use of gaseous ammonia was found to be most effective among the following bases (yields of 3a): AcONa (29%) $Et_3N$ (18%); KOH (17%); and KI (14%).

References


1) "Recent Advances in the Chemistry of β-lactam antibiotics", Ed. by J. Elks, Chem. Soc. Burlington House, London (1977). p. 101.

2) (a) S. Karady, L. M. Weinstock, F. E. Roberts, J. ten Broeke, R. F. Shuman, A. M. Hoinowski, S. H. Pines, and M. Sletzinger, Tetrahedron Lett., 1976, 2404; (b) H. Yazawa, H. Nakamura, K. Tanaka, and K. Kariyone, ibid., 1974, 3991 and references cited therein.

3) 7-Methoxy-analogue has been obtained from 3-exomethylenecepham by the action with t-BuOCl and MeOLi in THF (40% yield): G. A. Koppel, M. D. Kinnick, and L. J. Nummy, J. Am. Chem. Soc., 99, 2822 (1977). See also reference 1.

4) J. Gosteli, Chemia, 30, 13 (1976).

5) (a) S. Torii, H. Tanaka, N. Saitoh, T. Siroi, M. Sasaoka, and J. Nokami, Tetrahedron Lett., 22, 3193 (1981). A similar ene-type chlorination with $Cl_2$ and/or t-BuOCl has been reported: (b) R. D. G. Cooper, ibid., 21, 781 (1980); (c) M. Yoshioka, T. Tsuji, S. Ueyeo, S. Yamamoto, T. Aoki, Y. Nishitani, S. Mori, H. Satoh, Y. Hamada, H. Ishitobi, and W. Nagata, ibid., 21, 351 (1980).


(Received in Japan 9 February 1982)