Pergamon

Tetrahedron Letters, Vol. 35, No. 46, pp. 8691-8692, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01842-1

REDUCTIVE REARRANGEMENTS OF SILYLATED PENICILLIN G 1-OXIDE*

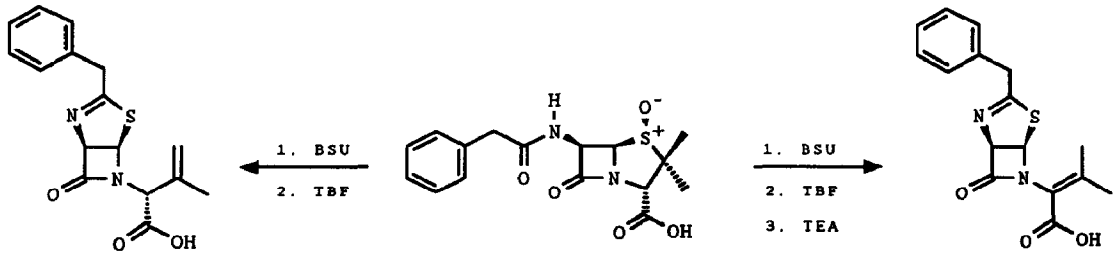
Pieter A.M. van der Klein, Henk A. Witkamp and Erik de Vroom*
Gist-brocades B.V., P.O. Box 1, 2600 MA Delft, The Netherlands

Abstract: The reaction of penicillin G 1-oxide with BSU followed by treatment with tributyl phosphite gives, after hydrolysis, crystalline thiazoline azetidinone **2**. Addition of triethylamine after reduction resulted in the formation of the isomeric thiazoline azetidinone **3**.

The Cooper rearrangement[1] is a well known procedure for the synthesis of thiazoline azetidinone **2** from penicillin G. Compound **2** can be converted into valuable 3'-norcephalosporin antibiotics such as Ceftibuten[2]. In its original form, the reductive rearrangement is performed on esters of penicillin G 1-oxide. This requires two separate steps and the use of expensive carboxylic acid protective groups such as 4-methoxybenzyl, 4-nitrobenzyl or diphenylmethyl. In our search for cheap and simple processes for the preparation of intermediates for cephalosporin antibiotics we have investigated a one-pot procedure for the synthesis of **2** using *in situ* silyl protection of the carboxylic acid function.

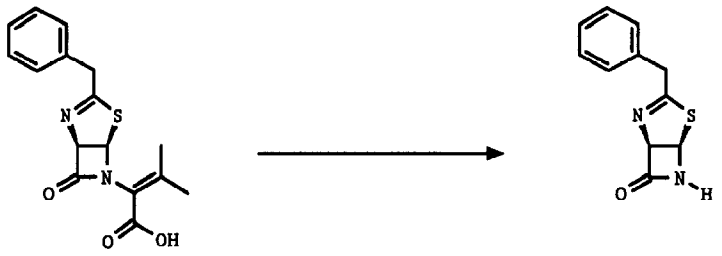
Based on earlier work on the acid-catalyzed ring expansion of penicillin G 1-oxide into 3'-deacetoxycephalosporin[3], we reasoned that treatment of penicillin G 1-oxide (**1**) with bis(trimethylsilyl)urea (BSU) would be a mild way to silylate the penicillin carboxylic acid moiety. Subsequent reduction with a trialkyl phosphite followed by hydrolysis would give the desired thiazoline **2**. Indeed, treatment of anhydrous penicillin G 1-oxide (**1**) with BSU in toluene followed by reduction with tributyl phosphite at reflux gave, after addition of water, the required compound in crystalline form in 65% yield based on **1** (not optimized)[4].

The 3-methyl-2-butenoic acid thiazoline azetidinone derivative **3** is a key intermediate in the synthesis of β-lactam derivatives having modifications that cannot be prepared by means of manipulating the penicillin 5-membered thiazolidine ring or the cephalosporin 6-membered dihydrothiazine ring. The butenoic acid moiety of **3** can, in principle, be removed by ozonolysis followed by base-catalyzed hydrolysis[5] or electrolysis[6]. The NH-function of the resulting compound **4** can serve as starting point for the construction



(2) (1) (3)

* On the occasion of the 25th anniversary of Dr. J. Verweij at Gist-brocades.



(3) (4)

of new 5- or 6-membered rings[7]. As was the case with **2**, the preparation of **3** from **1** has only been reported using carbon esters of the carboxylic acid function[5,8]. It occurred to us that the one-pot silylation/reduction procedure described above could also be applied towards the synthesis of **3**, provided a base-induced isomerization is included in the reaction sequence. Thus, treatment of silylated **1** with tributyl phosphite as described above, followed by the addition of triethylamine indeed gave, after work-up, crystalline **3** in 77% yield (not optimized)[9].

The results presented here indicate the possibility for the development of inexpensive high yielding one-pot procedures for the synthesis of thiazoline azetidinone derivatives **2** and **3**. These compounds can serve as intermediates for a variety of β-lactam antibiotics having structural modifications.

Acknowledgement

The authors whish to thank Mr. M.M. Poot for recording the ^{1}H NMR spectra.

References and notes

1. R.D.G. Cooper and F.L. Jose, *J. Am. Chem. Soc.* **1970**, *92*, 2575.
2. M. Yoshioka, *Pure Appl. Chem.* **1987**, *59*, 1041.
3. J.J. de Koning, H.J. Kooreman, H.S. Tan and J. Verweij, *J. Org. Chem.* **1975**, *40*, 1346.
4. 50.0 g (purity 97.9%; 140 mmol) of **1** and 50.0 g (245 mmol) of BSU were heated in 375 mL of toluene at 50 °C for 20 min. After cooling to 22 °C, 45 mL (161 mmol) of tributyl phosphite was added and the mixture was boiled under reflux for 40 min. At 30 °C, 250 mL of water was added and crystallization spontaneously started. The slurry was allowed to stand at 4 °C for 18 h after which yellow crystals were collected by filtration. Washing of the crystals with 125 mL water and 75 mL of butyl acetate gave, after drying under vacuum at 45 °C, 32.5 g colourless product (purity 89.0%, 91.4 mmol, yield 65.3%). 360 MHz ^{1}H NMR ($CDCl_3$): 1.67 ppm (s, 3H, CH_3), 3.86 ppm (s, 2H, $PhCH_2$), 4.73 ppm (s, 1H, $CHCO_2H$), 5.00 ppm (s, 1H, $C=CH_2$), 4.04 ppm (s, 1H, $C=CH_2$), 5.91 ppm (s, 2H, β-lactam), 7.3 ppm (m, 5H, Ph).
5. R.D.G. Cooper and F.L. Jose, *J. Am. Chem. Soc.* **1972**, *94*, 1021.
6. H. Tanaka, M. Taniguchi, Y. Noda, Y. Kameyama, M. Sasaoka, T. Shiroi and S. Torii, *Chem. Express* **1990**, *5*, 873.
7. L. Ghosez, J. Marchand-Brynaert, J. Vekemans, S. Bogdan and E. Cossement, *Tetrahedron* **1983**, *39*, 2493.
8. M. Narisada, H. Onoue, M. Ohtani, F. Watanabe, T. Okada and W. Nagata, *Tetrahedron Lett.* **1978**, 1755.
9. A mixture of 62.5 g (purity 97.9%; 175 mmol) of **1**, 62.5 g (306 mmol) of BSU, 56 mL (197 mmol) of tributyl phosphite, and 350 mL of butyl acetate was boiled under reflux for 90 min. 28 mL (200 mmol) of triethylamine was added and boiling was continued for 20 min. After cooling to 41 °C, 310 mL 0.5 M H_2SO_4 was added and the mixture was cooled to 3 °C. After stirring for 3 h crystals were collected by filtration. Washing of the crystals with 200 mL of water and 70 mL of butyl acetate gave, after drying under vacuum at 50 °C, 45.9 g cream white product (purity 92.4%, 134 mmol, yield 76.6%). 360 MHz ^{1}H NMR ($CDCl_3$): 1.59 ppm (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.85 ppm (ABq, 2H, $PhCH_2$), 5.95 ppm (s, 2H, β-lactam), 7.3 ppm (m, 5H, Ph).

(*Received in UK* 22 *August* 1994; *accepted* 16 *September* 1994)