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REACTION OF ACETOXYAZETIDINONES WITH TRIMETHYLSILYLACETYL THIOLESTERS: PREPARATION OF AZETIDINONE-THIOLESTER PRECURSORS TO CARBAPENEMS

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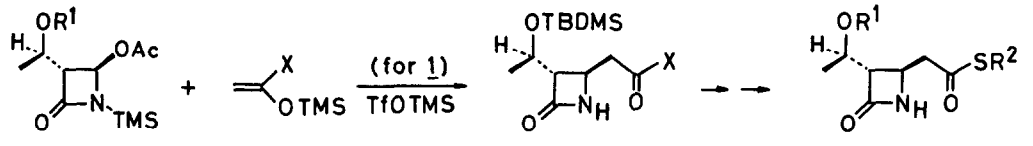
Summary: Reaction of acetoxyazetidinones, 1 and 2, with trimethylsilylacetyl thiolesters 10 afforded azetidinone-thiolesters, 11 and 12, which are useful intermediates in the carbapenem synthesis.

In a preceding paper,[1] we described a new method for construction of a carbapenem ring system by an intramolecular Wittig reaction of previously unknown trialkoxyphosphorane-thiolesters. The method can be applied not only to activated thiolesters but also to non-activated thiolesters which are difficult to cyclize by a usual intramolecular Wittig reaction[2] and provides a substitute for Merck's carbapenem synthesis involving a carbene insertion reaction.[3] We prepared various azetidinone-thiolesters 5, key compounds in the synthesis, in several steps from the ester 4a, which was easily obtained according to a procedure developed by Barrett and Quayle[4] from the acetoxyazetidinone 1 and silyl ketene acetal 3a in the presence of trimethylsilyl trifluoromethanesulfonate (TfOTMS). More conveniently, the phenyl thiolester 4b was obtained from 1 and silyl ketene thioacetal 3b by similar C-C bond formation reaction. For shortening the reaction steps, we required other silyl ketene thioacetals such as 7, a potential synthon for thienamycin synthesis. However, attempts to prepare 7 by applying the usual procedure[5,6] to a functionalized acetyl thiolester 6 [lithium diisopropylamide (LDA), THF, then TMSCl] have so far failed. Conse-



1: R^1=TBDMS
2: R^1=PNZ

3a: X=OCH_2Ph
3b: X=SPh

4a: X=OCH_2Ph
4b: X=SPh

5

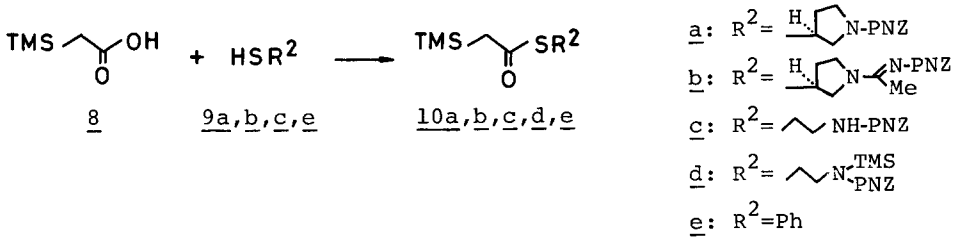
6

7

TBDMS: *t*-butyldimethylsilyl
PNZ: *p*-nitrobenzyloxycarbonyl
TMS: trimethylsilyl

quently, our attention was directed to the trimethylsilylacetyl thiolesters 10 which are supposedly equivalent to the silyl ketene thioacetals.[7] We report here a direct preparation of the azetidinone-thiolesters 5 (=11, 12) from the acetoxyazetidinones, 1 and 2, using the trimethylsilylacetyl thiolesters 10.

The requisite trimethylsilylacetyl thiolesters 10 were prepared from trimethylsilylacetic acid 8 and mercaptans 9 as follows. Reaction of the (*s*)-3-mercaptopyrrolidine derivative 9a[8] and trimethylsilylacetyl chloride, prepared from 8 by modification of the literature method,[9] afforded the desired thiolester 10a,[10] $[\alpha]_D^{22}$-12.4°(c=1.10, $CHCl_3$), in 38% yield. The thiolester 10b was prepared in 49% yield by the condensation reaction of the (*s*)-mercaptoamidino derivative 9b[8] and 8 using N,N'-dicyclohexylcarbodiimide (DCC) [4-(N,N-dimethylamino)pyridine (DMAP, trace), benzene, rt, 13 h] followed by purification with a Lobar column (E. Merck, Darmstadt). The mercaptan 9c was similarly esterified with 8 [DCC, DMAP (trace), benzene, rt, 5.5 h] to give the thiolester 10c, mp 49-50°C, in 61% yield. The NH group of 10c was protected by reaction with N,O-



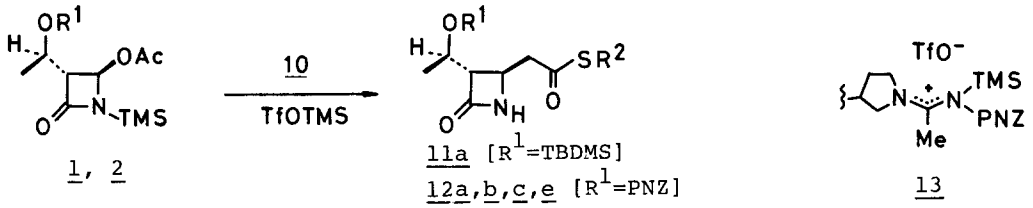
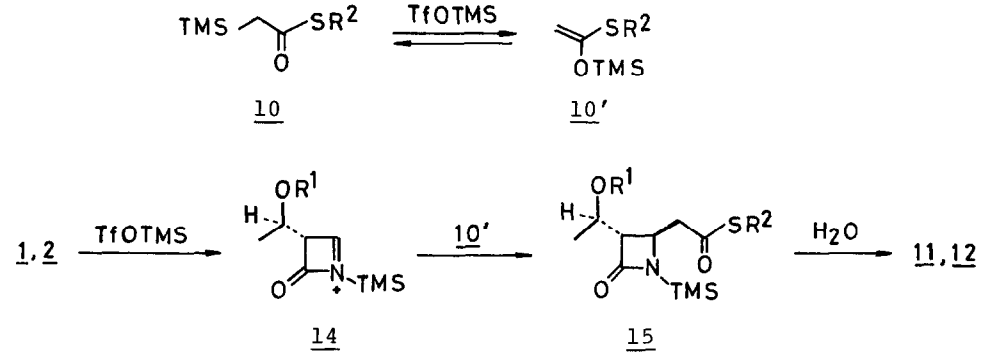


Table I. Reaction of Acetoxyazetidinones, 1 and 2, with Trimethylsilylacetyl Thiolesters 10a,b,d,e

Entry	Acetoxyazetidinone	Trimethylsilylacetyl thiolester (equiv)	TfOTMS (equiv)	Reaction Time (h)	Product	Yield (%)
1	1	10a (2)	0.14	15	11a	67
2	2	10a (2)	0.20	28	12a	87
3	2	10b (2)	0.20	14	12b	0
4	2	10b (2)	2.4	14	12b	58
5	2	10d (2)	0.28	24	12c	69
6	2	10e (1.5)	0.20	25	12e	93

bis(trimethylsilyl)trifluoroacetamide (3 equiv) [DMAP (trace), THF, rt, 30 h] to give N-trimethylsilyl derivative 10d in 96% yield after rapid silica gel chromatography. Phenyl thiolester 10e was obtained by reaction of thiophenol and trimethylsilylacetyl chloride (*ca.* 50%, diisopropylethylamine, methylene chloride, -15°C). The C-C bond formation reaction of the acetoxyazetidinones, 1 and 2,[11] with these trimethylsilylacetyl thiolesters 10 was carried out in methylene chloride in the presence of TfOTMS at room temperature. N-desilylation of the crude product was effected by treatment with a catalytic amount of pyridinium *p*-toluenesulfonate in THF-H_2O at room temperature to give the *trans* azetidinone-thiolesters, 11 and 12, in a moderate to high yield (Table I), which are identified by comparison with samples prepared from 4 as described in the previous paper.[1] In the reaction of 2 and 10b (Entry 3 and 4), excess TfOTMS was needed to perform the reaction, otherwise the desired product 12b was not formed probably due to consumption of the catalyst by forming the complex 13 with the basic amidino function of 10b. When the trimethylsilylacetyl thiolester 10e in the reaction with 2 (Entry 6) was replaced by the ketene thioacetal 3b, the same result was obtained (90% yield of 12e). This suggested that there was an equilibrium between the thiolester 10 and the silyl ketene thioacetal 10'. Treatment of the thiolester 10e with a catalytic amount of TfOTMS in $CDCl_3$ afforded an equilibrium mixture of 10e and 3b in approximately a 1 : 2 ratio (by NMR), confirming the equilibrium between 10 and 10'.



Thus, it is presumed that TfOTMS-catalyzed C-C bond formation reaction of the acetoxyazetidinones, 1 and 2, with the thiolester 10 proceeds *via* an electrophilic attack of the immonium intermediates 14 generated from 1 and 2 on the silyl ketene thioacetal 10' which is in an equilibrium with the thiolester 10. The reaction occurred exclusively at the sterically less hindered β-face of 14 to afford the *trans* azetidinone-thiolesters 15, of which hydrolysis led to the products 11 and 12.

Short-step transformation of these thiolesters, 11 and 12, into the carbapenems, *e.g.* thienamycin from 12c, *via* trialkoxyphosphorane cyclization was described in the preceding paper.

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7. Equivalency of the silyl ketene acetal and the α-silylacetyl ester was suggested by the fact that the silyl ketene acetal 3a underwent rapid isomerization to benzyl trimethylsilylacetate by treatment with TfOTMS. Recently, Lewis acid-catalyzed crossed aldol reaction using α-(trimethylsilyl)ketone instead of the silyl enol ether has been reported: B.A. Pearlman, J.M. McNamara, I. Hasan, S. Hatakeyama, H. Sekizaki and Y. Kishi, *J. Am. Chem. Soc.*, 103, 4248 (1981).
8. Mercaptans 9a and 9b were prepared according to a procedure developed by Drs. T. Miyadera and Y. Sugimura of these laboratories. See: Y. Sugimura, K. Iino, T. Shibata, T. Hashimoto, T. Tanaka, S. Sugawara and T. Miyadera, *Jpn. Kokai Tokkyo Koho* JP 84-13757, Jan. 24, 1984.
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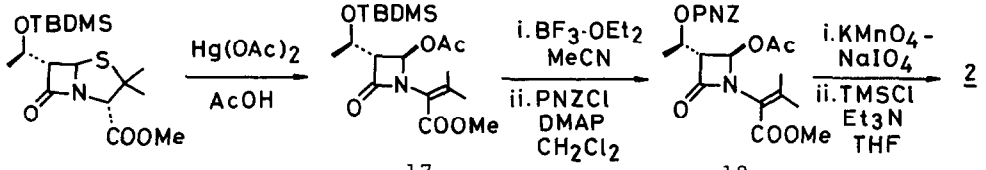
10. Experimental details for the preparation of 10a are as follows: a suspension of sodium trimethylsilylacetate in ether, obtained by mixing 8 (2 equiv) and NaH (2 equiv), was treated with oxalyl chloride (2 equiv) at 0°C for 15 min. To this mixture was added a solution of 9a (1 equiv) and diisopropylethylamine (2 equiv) in methylene chloride. After aqueous work-up, the product was purified by Lobar column chromatography. A major byproduct was a desilylated acetyl thiolester.
11. The optically active acetoxyazetidinone 2 was prepared from a penicillin-derived compound 16 by the following sequence of the reactions. Recently, preparation of 16 and 17 from 6-aminopenicillanic acid has been described



16 — 17 (mp 66-67°C) — 77% — 18 (mp 124-125°C) — 92%

in detail: W.J. Leanza, F. DiNinno, D.A. Muthard, R.R Wilkening, K.J. Wildonger, R.W. Ratcliffe and B.G. Christensen, *Tetrahedron*, 39, 2505 (1983).

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