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A MILD METHOD FOR THE CONVERSION OF PROPIOLIC ESTERS TO β-KETO ESTERS. APPLICATION TO THE FORMAL TOTAL SYNTHESIS OF (±)-THIENAMYCIN

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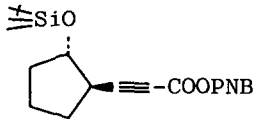
Summary: *An extremely mild method for the transformation of propiolic esters to β-keto esters via thiol addition is reported, including its successful application to the synthesis of (±)-thienamycin.*

In connection with studies directed toward the synthesis of β-lactam antibiotics, it was required to develop a extremely mild method for the conversion of a propiolic ester to a β-keto ester. In this communication, we wish to report a solution to this problem as well as its successful application to the synthesis of (±)-thienamycin.

The propiolic ester (1),[1] which would afford the quite unstable β-keto ester (2), was chosen as a suitable substrate for the present investigation. At first, the conversion of 1 to 2 was attempted according to the representative methods by using reagents such as $Hg(OAc)_2$-H_2SO_4[2] and Ag_2CO_3-AcOH,[3] affording none of the desired β-keto ester (2). Conversion initiated by the addition of piperidine, followed by acidic hydrolysis of the resulting enamine,[4] also did not give the desired product (2), resulting in the formation of the enone (3) in 50% yield together with 4 (13%).

It is generally known that the addition of a thiol to a propiolic ester takes place readily under the weakly basic conditions.[5] If a thiol adduct thus obtained can be converted to a β-keto ester under the mild conditions; for example, treatment with halogenating reagents such as *N*-bromosuccinimide (NBS) and *N*-bromoacetamide (NBA) in aqueous organic solvent, followed by reductive cleavage of a resulting halide,[6,7] a series of reactions would offer a mild method for the transformation of a propiolic ester to a β-keto ester. This was found to be the case. The addition of thiophenol[8] to the propiolic ester (1) readily occurred to afford the adduct (5)[9] in 98% yield, which was followed by treatment with NBA[10] in aqueous dioxane (dioxane-water, 10:1), resulting in the clean formation of the fairly unstable dibromide (6).[11,12] We were gratified to find that the β-keto ester (2) was efficiently generated by the simple addition of saturated Na_2SO_3 aq. solution in 68% yield. In addition to the extremely mild conditions, the present method is further characterized by the fact that the conversion of a propiolic ester to a β-keto ester can be carried out in " one-pot ". Typical experimental procedure is shown using the propiolic ester (7) with a β-lactam ring.

A mixture of the propiolic ester (7)[13] (201 mg, 0.05 mM), thiophenol (61 mg, 0.55 mM) and triethylamine (56 mg, 0.55 mM) in THF (2.8 ml) was stirred at room temperature for 3.3 hr under argon atmosphere. Evaporation of the solvent *in vacuo* afforded the oily residue, which



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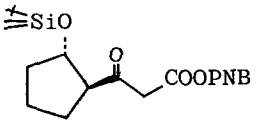

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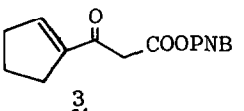

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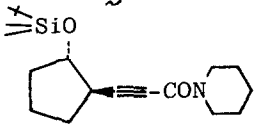

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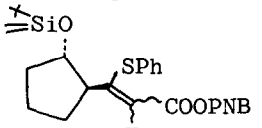

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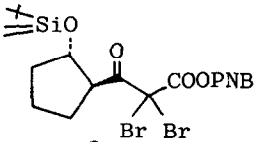

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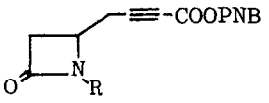
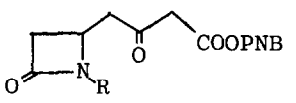


7: R=Si

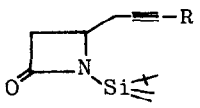
8: R=H



9: R=Si

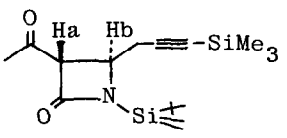
10: R=H

PNB=$-CH_2C_6H_4-NO_2-p$



11: R=H

12: R=$SiMe_3$



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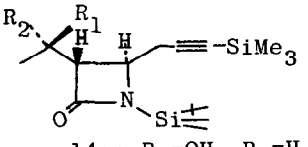
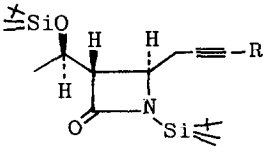


14a: R_1=OH, R_2=H

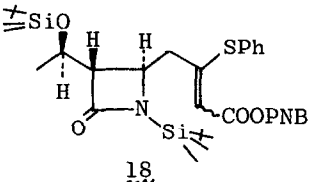
14b: R_1=H, R_2=OH



15: R=H

16: R=Li

17: R=COOPNB



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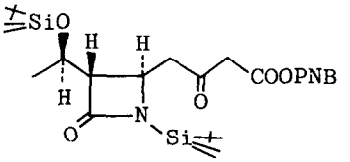

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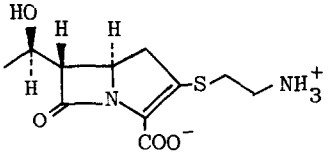

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was dissolved in 6 ml of aqueous dioxane (dioxane-water, 10:1). The solution was cooled to 0°C, and NBA (345 mg, 2.5 mM) was added. The solution was stirred for 0.5 hr under the same conditions, followed by the addition of saturated Na_2SO_3 aq. (6 ml). After stirring for 0.5 hr, the reaction mixture was warmed to room temperature. The product was extracted with ethyl acetate (20 ml x 3), and the combined organic extracts were washed with brine. Concentration of the dried solvent ($MgSO_4$) afforded the oily residue, which was purified by silica gel (20 g)

column chromatography (ethyl acetate-petr. ether, 1:2) to provide the desired β-keto ester (9)(166 mg, 79% yield) as a pale yellow oil: ν(max,$CHCl_3$) 1730, 1660, 1630, 1610, 1527, 1350, 840 cm-1; δ(ppm) 0.19 (3H,s), 0.22 (3H,s), 0.95 (9H,s), 2.64 (1H, dd, J=16 Hz, 2.5 Hz), 2.78 (1H, dd, J=18 Hz, 10 Hz), 3.15 (1H, dd, J=18 Hz, 4 Hz), 3.34 (1H, dd, J=16 Hz, 5.5 Hz), 3.58 (2H,s), 3.88 (1H,m), 5.29 (2H,s), 7.54 (2H, d, J=9 Hz), 8.23 (2H, d, J=9 Hz); MS(m/e) 421 (M^++1), 405, 363, 153, 136; HR-MS(m/e) 421.1809 (calc. for $C_{20}H_{29}N_2O_6Si$, 421.1794).

Similarly, in the case of the propiolic ester (8)[14] having an unprotected β-lactam ring, conversion to the β-keto ester (10) occurred efficiently in 66% yield.[15]

Further generality of this mild method was demonstrated by applying to the synthesis of (±)-thienamycin (20). The monosubstituted acetylene (11), obtained in 84% yield from 4-phenylsulfonylazetidin-2-one,[16] was first converted to the trimethylsilyl derivative (12) (LDA-Me_3SiCl) in 81% yield. Treatment of 12 with 2.5 equiv of LDA in THF provided the lithium enolate, which was added to 2 equiv of 1-acetylimidazole to give 13[17] in 79% yield. Reduction of 13 with KI-lithium selectride[18] in ether produced the alcohol (14a), mp. 87.3-88°C, and 14b in a ratio of 1.7 : 1[19] (87% yield). Protection of the hydroxy group as *t*-butyldimethylsilyl ether, followed by removal of the trimethylsilyl group by Schmidt's method,[20] furnished the terminal acetylene (15) in *ca.* 80% overall yield from 14a. The propiolic ester (17) was then produced by the gradual addition of the lithium acetylide (16)[21] to 2 equiv of *p*-nitrobenzyl chloroformate in THF at -78°C in 68% yield on the basis of the recovery of 15 (32%). With a sufficient amount of 17, mp. 124.8-126°C, in hand, crucial transformation to the β-keto ester (19), the known intermediate for the synthesis of thienamycin (20),[22] was attempted. As described above, treatment of the propiolic ester (17) with 1.1 equiv of thiophenol and 1.1 equiv of triethylamine in THF afforded the adduct (18), which was directly reacted with 6.4 equiv of NBA in aqueous dioxane (dioxane-water, 10:1) for 2.5 hr at 0°C. Reductive work-up including treatment with saturated Na_2SO_3 aq. solution provided the key intermediate (19), mp. 113-113.2°C, in 37% yield, which was identical with an authentic sample in every respect except for optical rotation.[22] Thus, a formal total synthesis of (±)-thienamycin (20) was accomplished by employing this newly-developed method for the transformation of a propiolic ester to a β-keto ester as a key step.

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References and Notes

1) The propiolic ester (1) was prepared by the gradual addition of the lithium acetylide generated from 21 to *p*-nitrobenzyl chloroformate in THF at -78°C in 78% yield.

2) P.F.Hudrlik and A.M.Hudrlik, Ed. by S.Patai, " The Chemistry of the Carbon-Carbon Triple Bond," Part 1. pp. 199-273, John Wiley & Sons, New York, N.Y., 1978.

3) Y.Ishino, I.Nishiguchi, S.Nakao, and T.Hirashima, Chemistry Lett., 641 (1981).

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5) J.I.Dickstein and S.I.Miller, Ed. by S.Patai, " The Chemistry of the Carbon-Carbon Triple Bond," Part 2, pp. 813-955, John Wiley & Sons, New York, N.Y., 1978.

6) For the reaction of a vinyl sulfide functionality with hypobromous acid, see D.F.Corbett,

J. Chem. Soc., Chem. Commun., 803 (1981).

7) For the reaction of a terminal acetylene with NBA in buffered aqueous acetic acid, see J.S.Mills, H.J.Ringold, and C.Djerassi, J. Am. Chem. Soc., 80, 6118 (1958).

8) The use of ethanethiol instead of thiophenol afforded the thiol adduct in unsatisfactory yield.

9) A mixture of the *E*- and *Z*-isomers (2:1 ratio); δ5.96 (Ha for the *E*-isomer), δ5.23 (Ha for the *Z*-isomer).

10) The use of NBS instead of NBA gave the unsatisfactory result.

11) The structure of the unstable dibromide (6) was determined by the spectroscopic data (mass and pmr spectra).

12) Under the conditions (mercuric chloride in methanol) reported by Carlson and Isidor, the reaction did not proceed. R.M.Carlson and J.L.Isidor, Tetrahedron Lett., 4819 (1973).

13) The propiolic ester (7) was prepared by the gradual addition of the lithium acetylide generated from 22 to *p*-nitrobenzyl chloroformate in THF at -78°C in 68% yield.

14) The compound (8) was prepared by treatment of 7 with hydrogen chloride in aqueous THF in 65% yield.

15) Under the conditions ($Hg(OAc)_2$-H_2SO_4-aqueous methanol), the propiolic ester (23) was converted to the β-keto ester (24) only in 28% isolated yield, see Ref. 16.

16) A.Nishida, M.Shibasaki, and S.Ikegami, Tetrahedron Lett., 4819 (1981).

17) The stereochemistry of 13 was determined by the PMR spectrum ($J_{Ha,Hb}$=2.5 Hz).

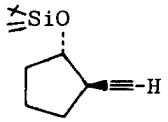
18) T.N.Salzmann, R.W.Ratcliffe, B.G.Christensen, and F.A.Bouffard, J. Am. Chem. Soc., 102, 6161 (1980).

19) The ratio was calculated by the PMR spectrum. Stereochemistry of 14a and 14b was determined by the method of Bouffard. F.A.Bouffard, D.B.R.Johnston, and B.G.Christensen, J. Org. Chem., 45, 1130 (1980).

20) H.M.Schmidt and J.F.Arens, Rec. Trav. Chim., 86, 1138 (1967).

21) The lithium acetylide (16) was prepared by the addition of 15 to LDA (1.8 equiv) in THF at -78°C.

22) T.N.Salzmann, R.W.Ratcliffe, F.A.Bouffard, and B.G.Christensen, Phil. Trans. R. Soc. Lond., B289, 191 (1980); D.G.Melillo, I.Shinkai, T.Liu, K.Ryan, and M.Sletzinger, Tetrahedron Lett., 2783 (1980): $\nu_{max}(CHCl_3)$ 2950, 2930, 2855, 1732, 1650, 1623, 1608, 1525, 1348, 1255, 1145, 838 cm^{-1}; δ(ppm) 0.05 (3H,s), 0.07 (3H,s), 0.20 (6H,s), 0.88 (9H,s), 0.95 (9H,s), 1.18 (3H, d, J=6.4 Hz), 2.85 (1H, dd, J=17.0 Hz, 8.0 Hz), 2.86 (1H, dd, J=4.5 Hz, 2.5 Hz), 3.03 (1H, dd, J=17.0 Hz, 4.9 Hz), 3.57 (2H,s), 4.03 (1H, ddd, J=7.9 Hz, 4.9 Hz, 2.5 Hz), 4.15 (1H, dq, J=6.1 Hz, 4.5 Hz), 5.30 (2H,s), 7.56 (2H, d, J=8.9 Hz), 8.27 (2H, d, J=8.9 Hz); MS(m/e) 579, 578 (M^+), 577, 563, 521, 503; HR-MS(m/e) 578.2841 (calc. for $C_{28}H_{46}N_2O_7Si_2$, 578.2843); Anal. calc. for $C_{28}H_{46}N_2O_7Si_2$: C, 58.10; H, 8.02; N, 4.84, Found: C, 58.32; H, 7.97; N, 4.74.



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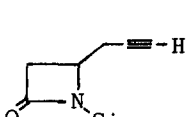

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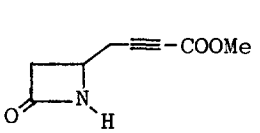

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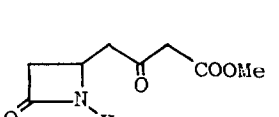

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