Communications to the Editor

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A SIMPLE METHOD FOR SYNTHESIZING 7-OXO-4-THIA-1-AZABICYCLO[3.2.0]-HEPTANE AND ITS 6-METHYL DERIVATIVES FROM ETHYL CYANOACETATE

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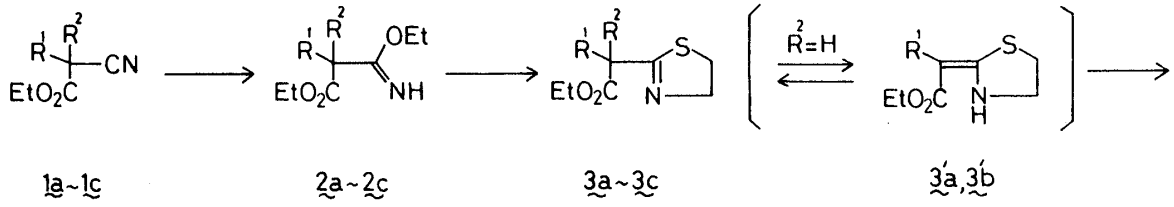
Ethyl cyanoacetate (1a) or its methyl derivatives (1b and 1c) were treated with HCl/EtOH to give the corresponding imidates (2a-2c). Treatment of the latter compounds with cysteamine gave ethyl 2-thiazoline-2-acetate (3a-3c), which by reduction with sodium cyanoborohydride in HCl/MeOH gave the corresponding thiazolidines (4a-4c). Hydrolysis followed by β-lactam formation through the use of Mukaiyama-Ohno's reagent afforded 7-oxo-4-thia-1-azabicyclo[3.2.0]heptane (6a) and its methylated derivatives (6b and 6c).

KEYWORDS —— penam; 6-substituted penam; sodium cyanoborohydrode; Mukaiyama-Ohno's reagent; 6-methyl-4-thia-1-azabicyclo[3.2.0]heptan-7-one; 6,6-dimethyl-4-thia-1-azabicyclo[3.2.0]heptan-7-one

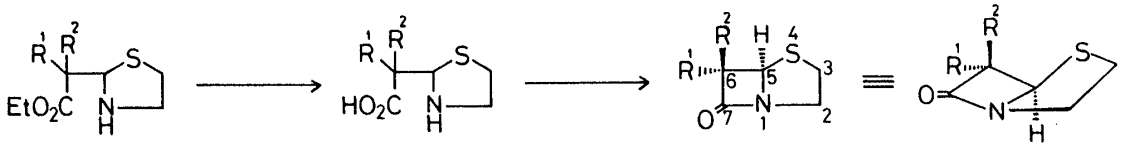
We have reported the synthesis of 7-oxo-4-thia-1-azabicyclo[3.2.0]heptane (6a), a so-called penam skeleton compound, from ethyl propiolate *via* thiazolidine-2-acetic acid (5a).[1] The key step in this synthesis was forming the β-lactam ring of the latter compound (5a) by using Mukaiyama-Ohno's reagent,[2] though the yield of 6a was very low (8%). This communication describes a general method for the synthesis of 5a and its 1'-methylated derivatives (5b and 5c) from ethyl cyanoacetate (1a) and their cyclization to the corresponding penams (6a-6c) using the same reagent. Two important experimental facts are revealed: the stereoselective ring closure of the 1'-methyl derivative of 5a (5b: a mixture of two diastereoisomers) to 6b (a single stereoisomer) and the strong dependency of the yields of 6a-6c upon the pattern of 1'-substituent in 5 and their causes are explained mechanistically.

The starting material in the present synthesis is ethyl cyanoacetate (1a). This compound was readily methylated at the 2-position by a base (KOH/EtOH) followed by the addition of MeI to give either the mono- or dimethyl derivatives (1b and 1c).[3] These ethyl cyanoacetates (1a-1c) were then treated with 1 mol eq of EtOH in ether saturated with HCl (0 °C, 5 days) to give the corresponding imidates (isolated as hydrochlorides: 2a-HCl;[4] mp 102-103 °C, 2b-HCl; mp 83-84 °C, 2c-HCl; mp 81-82 °C) in the yields of 95, 94, and 39%,[5] respectively. Treatment of the imidates (2a-2c, as hydrochlorides) with cysteamine hydrochloride in the presence of triethylamine (1.0 eq to 2) gave the corresponding thiazolines (3a;[6] mp 57-59 °C, 3b; oil, 3c; oil) in the respective yields of 65, 59, and 58%. Except for the dimethyl derivative (3c), both 3a and 3b existed as a tautomeric mixture (*ca.* 1:1 ratio) in $CDCl_3$. For example, the NMR spectrum of 3b showed the methyl

signal of the 3b-tautomer at δ 1.43 as a doublet (J=7 Hz) and that of the 3'b-tautomer at δ 1.80 as a singlet. Reduction of these thiazolines (3a-3c) by sodium cyanoborohydride in HCl/MeOH (0 °C, 0.5-1.5 h) gave the corresponding oily thiazolidines (4a,[1] 4b,[7] 4c) in 65, 54, and 45%[8] yields, respectively. While 4b was readily hydrolyzed by concentrated hydrochloric acid (room temp., 2 h) to 5b, as in the case of 4a to 5a,[1] hydrolysis of 4c was only possible with elevated temperature (70 °C, 4 h). The resulting acids were isolated as hydrochlorides [5a-HCl;[1] mp 103-105 °C, 5b-HCl; mp 89-91 °C (dec.), 5c-HCl; mp 82-84 °C (dec.)] in the respective yields of 50, 45, and 95% by evaporation of the solvent followed by trituration with ether-acetone.



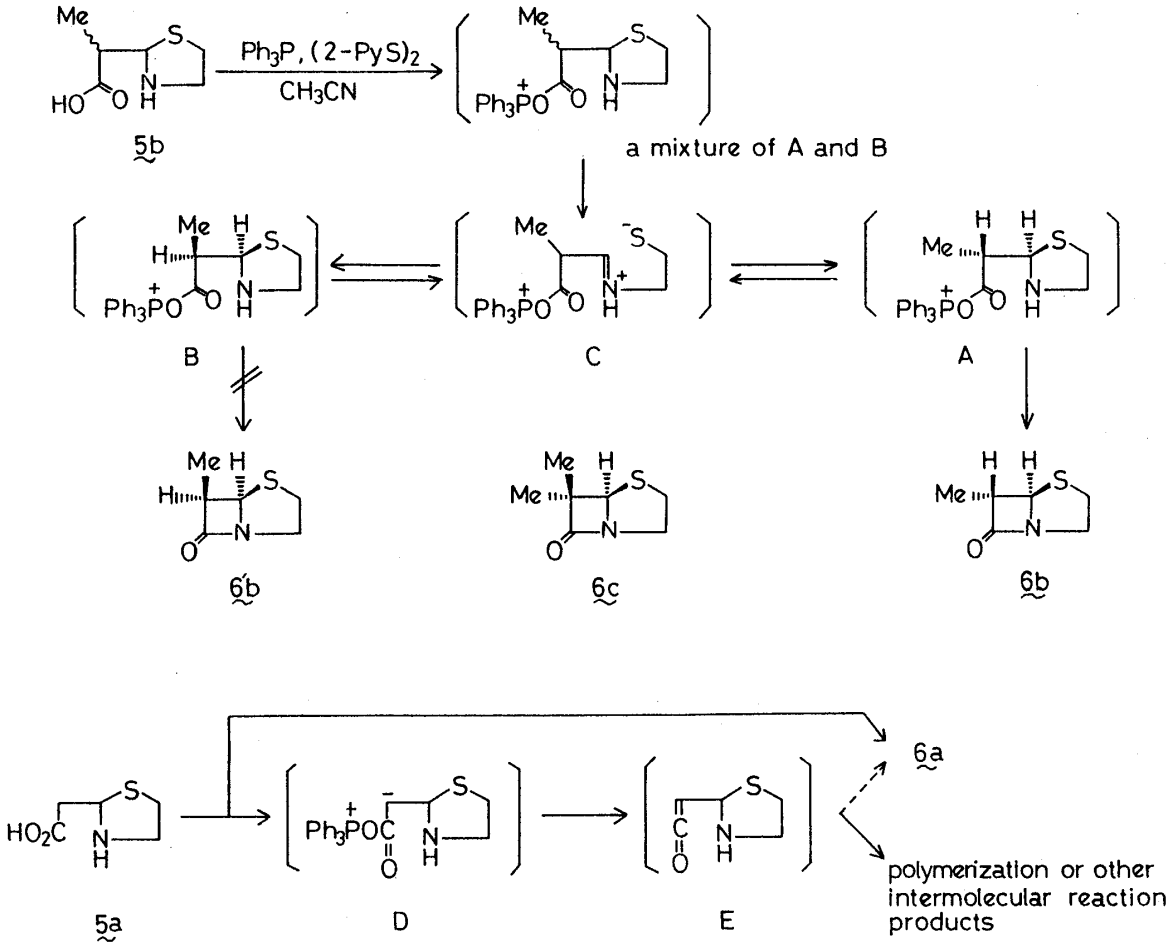
1a~1c 2a~2c 3a~3c 3'a,3'b



4a~4c 5a~5c 6a~6c

	a	b	c
R^1	H	Me	Me
R^2	H	H	Me

Treatment of 5b-HCl (a mixture of diastereoisomers;[7] *ca.* 1:1 ratio) with Mukaiyama-Ohno's reagent [0.01 M solution in CH_3CN in the presence of PPh_3 (1.2 mol eq), $(2\text{-Py-S})_2$ (1.2 mol eq), and Et_3N (1.0 mol eq), 0 °C, 4 h] gave 6b [oil, IR ($CHCl_3$): 1760 cm^{-1}. NMR ($CDCl_3$) δ: 1.42 (3H, d, J=7.5 Hz, CH_3), 2.65-3.30 (4H, m, $H_{2'}$, H_3, $H_{3'}$, and H_6), 4.15 (1H, ddd, J=10.5, 5.5, and 3.5 Hz, H_2), 4.62 (1H, d, J=1.4 Hz, H_5), high resolution MS m/z Calcd for C_6H_9NOS (M^+): 143.0404. Found: 143.0411] as the sole product, in 70% yield. A small coupling constant (J=1.4 Hz) between H_5 and H_6 in 6b indicates clearly the *trans* relationship between these two protons. This indicates that at least one diastereoisomer of 5b cyclizes to 6b with inversion of configuration at the 1'-position. Considering the fact that thiazolidine-2-acetates substituted by an alkyl group at the 2-position exist in tautomeric equilibria with the corresponding β-amino-crotonates, such equilibrium may also exist for the 2-unsubstituted thiazolidine-acetic acid derivatives.[9] Hence, the activated ester (A or B) may equilibrate *via* the iminium ion (C) between two diastereomers (A and B). Then only A cyclizes to 6b (thermodynamically more stable than 6'b), while B can not cyclize as such to 6'b but gives 6b *via* A.



Another noteworthy fact is that the presence of the methyl group at the 1'-position of 5 greatly enhances the yield of β-lactam (6). Thus, though upon treatment with Mukaiyama-Ohno's reagent 5a afforded only 8% of the β-lactam (6a),[1] 5b cyclized to 6b in 70% yield under the same reaction conditions. The difference in the two cyclization reactions may be explained as follows. That is, deprotonation from the activated ester or more possibly from the corresponding iminium ion (e. g., C) by a base (probably 2-PyS^-)[2] may only occur efficiently when the thiazolidineacetate is unsubstituted at the 1'-position. Such deprotonation would not occur readily when the 1'-position is substituted as A or B by a steric factor. Hence, only 5a is susceptible to the deprotonation under the cyclization reaction to give the carbanion (D) and this is transformed finally to the ketene (E). The latter then affords undesired products through intermolecular reactions typical of mono-substituted ketenes.[10] Since such ketene formation is impossible for 5c, 5c also cyclized to 6c [mp 34 °C, IR ($CHCl_3$): 1775 cm^{-1}. NMR (CCl_4) δ: 1.15 (3H, s, CH_3), 1.45 (3H, s, CH_3), 4.70 (1H, s, H_5). High resolution MS *m/z* Calcd for $C_7H_{11}NOS$: 157.0561. Found: 157.0563] in 71% yield.

The sequencial reactions described above provide not only another route to unsubstituted penam, but also a general and efficient method for the synthesis of 6-substituted penam derivatives.

REFERENCES AND NOTES

1) T. Chiba, J. Sakaki, T. Takahashi, and C. Kaneko, *Chemistry Lett.*, 1985, 659.

2) Mukaiyama's reagent, Ph_3P-(2-Py-S)$_2$, was originally used for peptide synthesis using CH_2Cl_2 or DMF as the solvent.[a,b] Recently, Ohno *et al.* used this reagent to form β-lactam compounds from β-amino acids and found acetonitrile as a solvent of choice for this reaction.[c] a) T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, 1970, 1901; b) T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.*, 15, 94 (1975); c) S. Kobayashi, T. Iimori, T. Izawa, and M. Ohno, *J. Am. Chem. Soc.*, 103, 2406 (1981).

3) The mono-methylated product (1b) was obtained by using 1a with the halide and base (each 1 eq) at 0 °C (4 h). The dimethylated product (1c) was best obtained *via* 1b (which could be used without isolation) by adding further amounts of the reagents: H. O. House, "Mordern Synthetic Reactions," 2nd ed., W. A. Benjamin Inc., California, 1972, p. 544.

4) A. Pinner and C. Oppenheimer, *Ber.*, 28, 478 (1895); G. Barnikow and G. Strickmans, *Chem. Ber.*, 100, 1428 (1967).

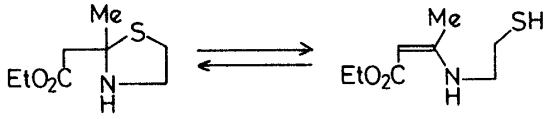
5) A significant amount of 1c was recovered under these conditions.

6) R. Kuhn and F. Drawert, *Ann. Chem.*, 590, 55 (1954).

7) The ester (4b) is a mixture of two diastereoisomers at the 1'-position as evidenced from the NMR spectrum (δ: $CDCl_3$): 1.31 (1/2×3H, d, J=7 Hz, CH_3), 1.34 (1/2×3H, d, J=7 Hz, CH_3), 4.62 (1/2×1H, d, J=9 Hz, 2-H), 4.65 (1/2×1H, d, J=7 Hz, 2-H). The same is also true for the corresponding acid (5b).

8) The starting material (3c) was recovered in 19% yield.

9) Ethyl 2-methylthiazolidine-2-acetate exists in tautomeric equilibria with the corresponding β-aminocrotonate (F⇄G).[a] Hence it is reasonably assumed that such equilibrium also exists in 2-unsubstituted thiazolidines.[b]



F G

In accordance with this explanation, 4b showed a single spot on TLC and attempts to separate it into two diastereoisomers were unsuccessful. a) P. S. Farmer, C-C. Leung, and E. M. K. Lui, *J. Med. Chem.*, 16, 411 (1973); b) R. Tondeur, R. Sion, and E. Peray, *Bull. Soc. Chim. Fr.*, 10, 2493 (1964).

10) Reactivity of ketenes towards polymerization or intermolecular reaction with nucleophiles decreased in the order of CH_2=C=O > RHC=C=O > RR'C=C=O: see, W. T. Brady, "The Chemistry of Ketenes, Allenes and Related Compounds," Part 1, ed. by S. Patai, John Wiley and Sons, Inc., New York, 1980, Chapter VIII.

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