Tetrahedron Letters, Vol.22, No.22, pp 2109 - 2112, 1981
Printed in Great Britain

0040-4039/81/222109-04$02.00/0

C-C BOND FORMATION FROM SCHIFF BASE AND VINYLOXYBORANE: SYNTHESIS OF β-AMINO ACID DERIVATIVES

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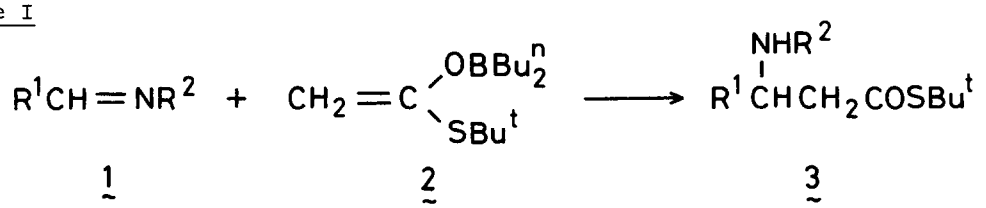
Summary: An efficient methodology for the preparation of β-amino acid derivatives (3) by C-C bond formation from Schiff bases (1) and vinyloxyborane (2) and their utilization in the synthesis of the pyrimidine moiety (3f) of bleomycin are described.

In a recent communication,[1] we reported on the synthesis of the pyrimidine moiety of bleomycin, an effective antitumor antibiotic.[2] The key feature of the approach includes C-C bond formation at the C=N double bond of a Schiff base 1f with malonic half ester. However, the malonic half ester method always accompanied unsaturated ester,[3] and the ethoxycarbonylmethyl group was introduced in rather low yields. The requirements for the introduction of an alkoxycarbonylmethyl group at the C=N double bond of Schiff bases are indeed demanding in the elaboration of complex β-amino acid moiety contained in bleomycin congeners[4] and also in the synthetic extension of Schiff bases. It was considered that the vinyloxyboranes first applied to carbonyl compounds by Mukaiyama[5] might provide a solution for this problem.

We wish to describe here an efficient methodology for the preparation of β-amino acid derivatives based on the use of vinyloxyborane (Scheme I). This method requires very mild reaction conditions and is applicable satisfactorily to a variety of Schiff bases prepared from aldehydes and amines as shown in Table I.

Scheme I



1 2 3

Scheme II

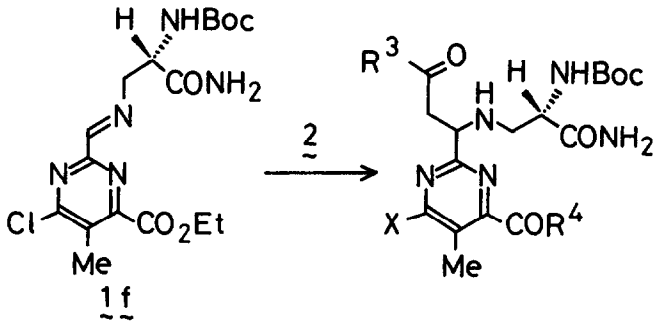
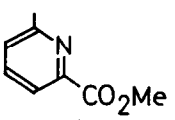
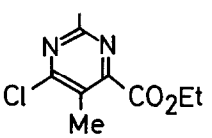


Table I. Reaction of Schiff Bases (1) and Vinyloxyborane (2)

	Schiff Base 1[a] R^1	R^2	Solvent	Product 3[b,12] Yield %
a	Ph-	$PhCH_2$-	Et_2O	80, oil
a	Ph-	$PhCH_2$-	THF	35
a	Ph-	$PhCH_2$-	CH_2Cl_2	33
a	Ph-	$PhCH_2$-	Toluene	26
b	PhCH=CH-	$PhCH_2$-	Et_2O	63, oil
c	Ph-	MeO_2CCH_2-	Et_2O	52, oil
d	Ph-	$MeO_2C(CH_2)_2$-	Et_2O	86, oil
e		$MeO_2C(CH_2)_2$-	Et_2O	81, oil
f		NHBoc CH_2-C-$CONH_2$ (S)	Et_2O	40, foam
g	Et-	$PhCH_2$-	Et_2O	43
h	^{i}Py	$PhCH_2$-	Et_2O	45

[a]The Schiff bases 1a-1h were prepared by distillation under a reduced pressure from the corresponding aldehydes and amines, and 1e and 1f were prepared in the presence of activated molecular sieve (3Å) and directly reacted with vinyloxyborane. [b]Yields are based on purified products and have not been optimized.

The representative C-C bond formations by the use of vinyloxyborane were carried out according to the following general procedure. To about equimolar quantities of di-n-butylboryl trifluoromethanesulfonate and diisopropylethylamine (1.1 equiv), as a 0.5 M solution in anhydrous ether at 0°C under argon atmosphere, tert-butyl thioacetate (1.0 equiv) dissolved in anhydrous ether (0.5 M solution) was added gradually dropwise, and the reaction mixture was kept at 0°C

for 30 min with stirring, indicating enolate formation by precipitation of white amine triflate. The resultant enolate solution was treated with a Schiff base 1a (0.8 equiv) dissolved in anhydrous ether (0.5 M solution). The reaction mixture was warmed to room temperature (30 min) and allowed to stand at room temperature for 1 h. The resultant boron chelate of 3a was most efficiently oxidized to β-amino thioester 3a by treatment with 30% H_2O_2 at 0°C for 30 min. In our hands, the hydrogen peroxide procedure was superior to the molybdenum peroxide method.[6] The ethereal solution was washed with 1 N aqueous sodium hydroxide solution and after usual workup, the reaction products were subjected to tlc, affording 3a in excellent yield.

Although no optimization of the yields was attempted, ether was found to be the best solvent for the C-C bond formation, and tetrahydrofuran, methylene chloride and toluene were found to be poor solvents.

As for the C-C bond formation from Schiff bases, Grignard and Reformatsky reactions[7,8] and the use of organolithium compounds[9] are known. The Grignard reaction and the organolithium compounds afford simply alkylation products, and the Reformatsky reaction affords generally β-lactam compounds and requires higher temperatures (in benzene or toluene under reflux). Treatment of the Schiff base 1f[1] with ethyl bromoacetate and zinc[8a] afforded no expected β-lactam compound showing decomposition of such sensitive Schiff base 1f under the Reformatsky conditions.

However, vinyloxyborane reacts smoothly even with the sensitive and complicated Schiff base 1f,[11] affording 3f in reasonable yield higher than the malonic half ester method.[1] Thus, the pyrimidine moiety of bleomycin has become more easily available by the application of the present methodology as shown in Scheme II. The introduction of methoxycarbonylmethyl at the C=N double bond of 1f was carried out using a large excess of 2 (4.5 equiv) to give 3f. The thioester group was untouched by treatment with 0.1 N NaOH (2 equiv) in CH_3CN) at 0°C for 1 h hydrolyzing only the ethyl ester group to afford 3i in 77%[12] yield. The thioester and chloro groups of 3i afforded pyrimidoblamic acid,[1] a key intermediate in belomycin synthesis,[1] easily in good yield by treatment with ammonia at 40°C for 3 days in EtOH.

It may be reasonable to postulate that the reaction proceeds via a pericyclic process like that of the aldol condensation.[10] The generality of the present reaction and the application to other biologically active compounds will be reported in due course.

Acknowledgment: We express our gratitude to Prof. H. Umezawa of the Institute of Microbial Chemistry for his encouragement, and this work was financially supported in part by Grants-in-aid for Special Project Research from the Ministry of Education, Science and Culture of Japan.

References and Notes

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2. Bleomycin is an antitumor antibiotic first reported in 1966 and clinically used in the chemotherapy of squamous cell carcinomas and malignant lymphomas, see H. Umezawa, Heterocycles, 13, 30 (1979), and reference cited therein.
3. The unsaturated esters were essentially consisted of E-form and considered to be formed by simultaneous decarboxylation and deamination presumably from threo isomers after C-C bond formation.
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11. The Schiff base 1f was prepared from ethyl 6-chloro-2-formyl-5-methylpyrimidine-4-carboxylate[1] and (S)-3-amino-2-[(tert-butoxycarbonyl)amino]propionamide[1] in the presence of activated molecular sieve in ether at room temperature.
12. The compound 3f was found to be an epimeric mixture in about equal amounts by introducing to 3i as described in our previous communication,[1] and all materials gave mass (field desorption) and NMR (^{13}C and ^{1}H) spectra consistent with their structure.

(Received in Japan 28 February 1981)