A Novel Synthesis of Chiral 1-Allyl-1,2,3,4-tetrahydro-β-carboline Employing Allyltributyltin and Chiral Acyl Chlorides

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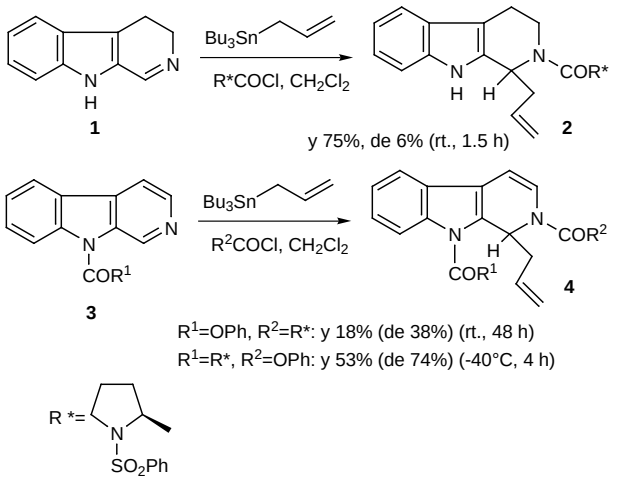
Abstract: β-Carboline was acylated at its 9-position by a chiral acyl chloride, followed by reaction with allyltributyltin and 2,2,2-trichloroethyl chloroformate to afford an 1-allyl-1, 2-dihydrocarboline derivative in a diastereoselective manner. The chiral acyl group at *N*-9 was readily eliminated by aqueous alkali to give carboxylic acid quantitatively without racemization on C-1 position. The formed 1-allyl-1,2-dihydro-β-carboline was transformed to 1-allyl-1,2,3,4-tetrahydro-β-carboline.

Key words: β-carboline, allyltributyltin, asymmetric addition, chiral acyl chloride, 2,2,2-trichloroethyl chloroformate

Introduction of allyl group to organic compounds is one of the major subjects of organic synthesis[1] due to ready transformation of allyl group into other functional groups. In the course of our study on the reaction of *N*-acylated azaaromatics, we found that allyltributyltin is a versatile nucleophile toward a variety of azaaromatics without side reactions with coexisting acyl chlorides.[2] This result prompted us to investigate an asymmetric allyl addition toward azaaromatics, and it was found that β-carboline having a chiral acyl group at *N*-9 position is a good substrate for the asymmetric addition of allyltributyltin at C-1, and the adduct thus formed is readily transformed to 1-allyl-1,2,3,4-tetrahydrocarboline in good yields. This paper describes the results.

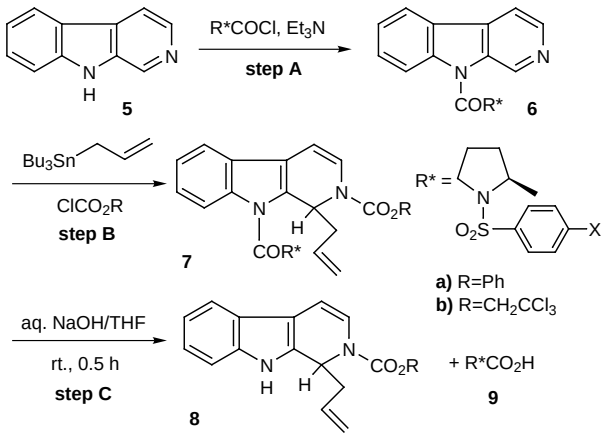
1-Substituted-1,2,3,4-tetrahydro-β-carboline moiety is one of the most universal parent structures in alkaloids, and there are a lot of reports concerning its synthesis.[3] Most of these studies adopted 3-(2-aminoethyl)indole derivatives as starting materials, and the subjection to Pictet-Spengler reaction afforded the nucleus.[4] In contrast, there are few examples in which the 1,2-unsaturated β-carboline moiety was directly derivatized by addition reaction of nucleophiles to give tetrahydro-β-carboline derivatives, and these limited examples treated almost exclusively the introduction of allyl groups. Martin *et al*.,[5] and Yamaguchi *et al*.,[6] reported that 3,4-dihydro-β-carboline was subjected to addition reaction of nucleophiles in the presence of acyl halides to give 1-substituted tetrahydro-β-carboline derivatives. In these reactions, *N*-acylated iminium salts formed *in situ* were trapped by silyl enol ethers or organotin reagents.[7] There has been, however, only an asymmetric version of these reactions reported so far.[8] There has been only one type of general asymmetric induction to the tetrahydro-β-carboline framework, that is, Meyers *et al*. developed lithiation of tetrahydro-β-carboline having *O*-tert-butylvalinol formamidine moiety at the N-2 position, and subsequent alkylation resulted in high diastereo excess (de) of the reaction products.[9]

In a previous paper, we reported that an acyl chloride derived from simple amino acid afforded high de in the 1,2-addition of silyl enol ethers to the isoquinoline nucleus.[10] Thus, we investigated the application of the system to β-carboline derivatives. Although the first application of 1,2-addition was simply carried out using 3,4-dihydro-β-carboline, a chiral acyl chloride, and allyltributyltin according to the reported procedures,[5-7] there resulted in almost no stereoselectivity in spite of moderate chemical yields. One of the examples is shown in Scheme 1 (**1**→ **2**).[11] An addition to the aromatic β-carboline **3** also resulted in a low yield and low de of the product formation shown. To our surprise, however, the exchange of two acyl groups raised the de considerably (Scheme 1). In the reaction, 9-[*N*-(phenylsulfonyl)prolinyl]-β-carboline was treated with allyltributyltin and phenyl chloroformate to give the adduct **4** in 53% yield and 74% de.



Scheme 1

Consequently, it was found that the chiral auxiliary was more effective at N-9 in spite of one atom farther than N-2. The chiral auxiliary used was readily removed by the treatment of **4** with aqueous NaOH/THF for 30 min at room temperature.



Scheme 2

Thus we investigated using various chiral acyl chlorides and chloroformates to optimize the reaction conditions. Acylation of the N-9 position by various acyl chlorides derived from *N*-sulfonyl proline derivatives[12] resulted in almost quantitative yields of compound **6** in Scheme 2 (step A).[13] Thus the addition of allyltributyltin was investigated using various acyl groups at N-9 in CH_2Cl_2,[14] whose results are summarized in Table 1.

Table 1 Reaction of 9-Acyl-β-carboline **6** with Allyltributyltin in the Presence of Phenyl Chloroformate

Entry	X	Time (h)	Yield of **7**(%)	Yield of **8** (%)	% ee of **8**[a)]
1	H	4	53	97 (83)[b)]	74
2	4-NO_2	16	99	96 (90)	67
3	4-MeO	5	95	86 (85)	69
4	4-Cl	5	99	91 (96)	72
5	4-I	5	90	99 (95)	68
6	4-Me	6	99	99 (95)	75
7	4-*i*-Pr	5	90	99 (94)	77
8	4-*t*-Bu	3	95	88 (99)	78
9	4-*t*-Am	4	90	95 (88)	80
10	3-NO_2	24	99	98 (94)	64
11	2,3-benzo	4	92	96 (99)	60
12	3,4-benzo	5	73	99 (90)	51

a) Determined by HPLC using Chiralcel OD column.
b) The recovery of **9** (%) was shown in the parenthesis.

The results show that the adducts **7** were obtained quantitatively, and the recovery of the chiral auxiliary also proceeded smoothly. It was suggested from these data that the substituent at the para position of the phenylsulfonyl group has a slight influence on the stereoselectivity, and a bulky *t*-amyl group gave a superior result (Table 1, entry 9).

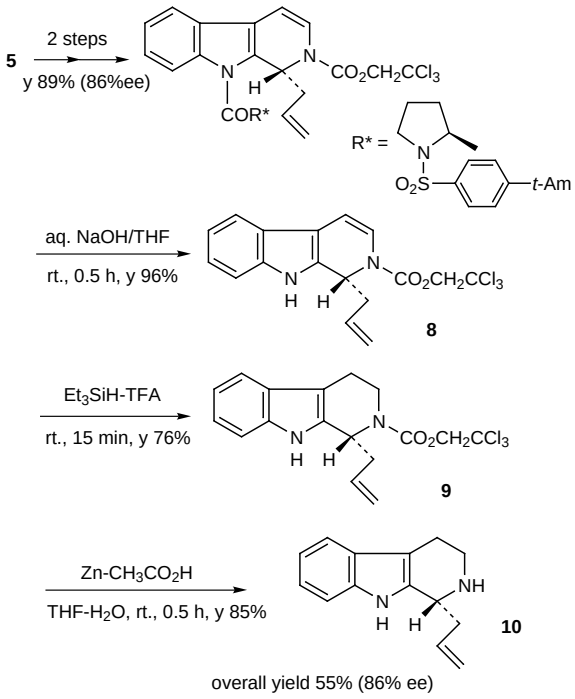
Accordingly, the other reaction condition was investigated using *N*-[*p*-(*t*-amyl)phenylsulfonyl]-L-prolinyl group as the chiral auxiliary, and the results are summarized in Table 2.

Among the activators, 2,2,2-trichloroethyl chloroformate was most reactive, and the reaction could be carried out at –78°C. The ee of **8** was up to 86%.

Table 2 Reaction of 9-[*N*-[*p*-(*t*-amyl)phenylsulfonyl]prolinyl]-β-carboline with Allyltributyltin in the Presence of Various Chloroformates

Entry	R	Temp(°C)	Time (h)	Yield of **7**(%)	Yield of **8** (%)(%ee)
1	Ph	-40	4	90	95 (80)
2	Et	-40	5	36	98 (59)
3	CH_2CCl_3	-40	2	94	96 (81)
4	CH_2CCl_3	-78	24	62	96 (84)
5	CH_2CCl_3	-78	24	84	96 (86)
6	CH_2CCl_3	-78	48	98	96 (86)

The obtained **8** (Scheme 3) was allowed to be reduced with triethylsilane-trifluoroacetic acid (TFA) to give 3,4-dihydro derivative **9**, and the trichloroethyl group was eliminated by Zn-CH_3CO_2H to give 1-allyl-1,2,3,4-tetrahydro-β-carboline (**10**) in 86% ee.[15] The overall yield of **10** from the parent **5** was 55% (86% ee) *via* 5 steps.



Scheme 3

The absolute configuration of **10** was determined as *R* by the derivatization of **10** to 1,2,3,4-tetrahydro-9-methoxymethyl-2-(*trans*-2,4-pentadienoyl)-β-carboline,[16] which was reported as an intermediate for the total synthesis of (+)-pseudoyohimban.[9b]

In this paper, we described the synthesis of chiral 1-allyl derivative of 1,2,3,4-tetrahydro-β-carboline using a readily available amino acid as a chiral auxiliary. The allyl group is thought to be a versatile synthetic tool for diverse kinds of alkaloids, and the syntheses of some natural products are now in progress.

References and Notes

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(8) Yamaguchi *et al*. reported in a review that benzyl 3,4-dihydro-β-carboline-3-(*S*)-carboxylate underwent the addition reaction with acryloyl chloride and tributyl(2,4-pentadienyl)tin to give yohimban derivatives in 83% yield (86% de). Yamaguchi,R. *Yuki Gosei Kagaku Kyokaishi*, **1991**, *49*, 128.

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(11) Compound **1** could not be acylated at N-9 under usual conditions, thus the experiment parallel to **3** → **4** could not be carried out.

(12) Other amino acids such as alanine, phenylalanine, valine, etc., were used for the reaction, but the de at step B was lower than that of proline derivatives.

(13) Step A of Scheme 2 proceeded by the use of one eq. of acyl chloride and two eq. of triethylamine in THF at room temperature for 2-4 h. All the isolated yields were above 80%, and the details will be reported in a near future.

(14) The other solvents such as 1,2-dichloroethane, acetonitrile, toluene, and DMF were used for the reaction, and dichloromethane was found to afford the best results.

(15) The ee was monitored on a chiral HPLC, and it was found that no racemization occurred in the transformation of **8** to **10**.

(16) Compound **10** was treated with *trans*-2,4-pentadienoic acid and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide in CH_2Cl_2 to give 1-allyl-1,2,3,4-tetrahydro-2-(*trans*-2,4-pentadienoyl)-β-carboline in 75% yield. The compound was allowed to react with methoxymethyl chloride in the presence of potassium hydride to give the product without racemization.

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