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Solid Phase Synthesis of β - Carbolines

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Abstract: Synthesis of β-carbolines on solid phase using TCCA as the key reagent is developed.

Keywords: Solid phase synthesis, β-carbolines, TCCA.

Much attention has been paid to carbolines in recent years, owing to the wide range of their biological activity [1]. Many papers have reported the synthesis and reactivity of carbolines[2,3].

Generally there are two ways to synthesize carbolines. One is through the Bischler-Napieralski reaction, and the other through Pictet-Spengler reaction. In the former method, the reaction of carboxylic acids with tryptophan using PPE or $POCl_3$ as the condensing agent give dihydro-ß-carbolines, which are convertible readily to ß-carbolines. Though there were examples in the literature, using $POCl_3$/80℃ to prepare the resin bound-dihydroisoquinolines in good yield and purity[4], it didn't give dihydro-ß-carboline with satisfactory purity.

We selected the P-S reaction in our study. Although the tetrahydro-ß-carboline can be easily obtained by the reaction of tryptophan with aldehydes, the subsequent aromatizing step is always troublesome. It is the key issue in the solid phase synthesis of carbolines. There are many methods for dehydrogenation of tetrahydro-ß-carbolines, including DDQ, SeO_2, MnO_2 and Pd/C[1]. But none of them is satisfactory, either because of the harsh reaction conditions or unstable yield. During the course of our study, TCCA (trichlorocyanuric acid) as a mild dehydrogenating reagent was reported[5]. We successfully applied this agent to the solid phase synthesis.

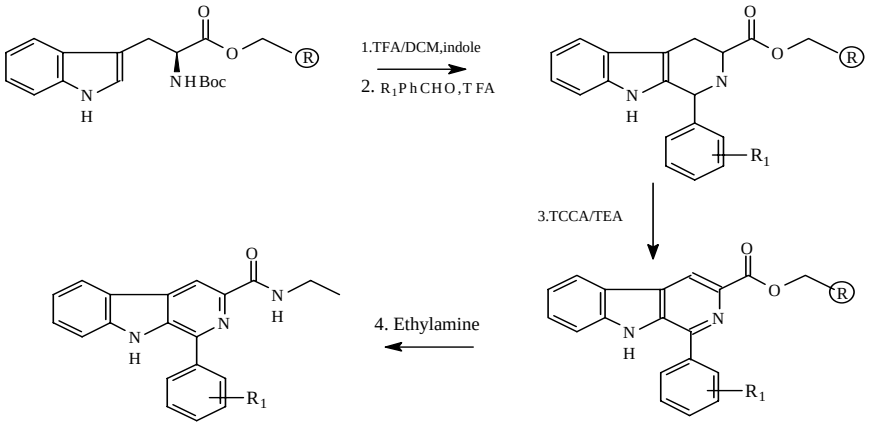
The resin-bound tryptophan was treated with a solution of aldehyde and TFA in methylene dichloride to form the polymer supported tetrahydro-ß-carbolines[6]. After careful washing to remove the excess acid, the resin was reacted with TCCA/TEA under low temperature to give the fully aromotized carbolines. The corresponding carbolines were obtained after cleavage from the resin with a solution of ethylamine in THF. The results are shown in **Table 1**.

The results demonstrated the feasibility of solid phase preparation of ß-carbolines. Because of the mild conditions, it could be used in combinatorial chemistry. Further study is in progress.

Table 1. Result of the solid phase synthesis

Entry	R_1-	purity %[7]	HPLC[7] CH_3OH%	MS	Yield%
1	H	68.9	70	315	69.4
2	3,4-OCH_2O	82.5	70	359	73.6
3	2-Cl	55.8	70	346	67
4	4-Br	82.7	60	393/395	79

Scheme 1



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Reference and notes

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7. Analysis by HPLC (4. 6 X 250mm, RP-18, 5 μ m particle size, eluting by CH_3OH/H_2O, 1. 0ml/min) by area integration at 254 nm.
8. A typical procedure for the dehydrogenation of tetrahydro-ß-carboline is as follows: aldehyde and TFA were added to a solution of resin bound Trp in DCM and the resulting mixture is cooled to – 20℃, subsequently TCCA dissolved in DMF was slowly added, then shaken at 0 ℃ for 1 hr and 10℃ for 2 hrs. The solution was drained and the resin washed with DCM, DMF. To the resin was added EA/ THF and the mixture was shaken overnight. The resin was filtered and the solution was evaporated to dryness to give the corresponding ß-carboline.

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