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NOTE

Microwave-Assisted Synthesis of Taxol Side-Chain Precursor from Malonic Acid

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Being a complex diterpenoid, the potent anticancer drug, taxol requires complicated multistep for its synthesis. Due to the chemical complexity of taxol, its commercial production by total synthesis is not likely to be economical. Another natural product, 10-deacetyl baccatin 111 is readily available in higher yield. Several methods have been reported for the synthesis of taxol by coupling baccatin 111 and the *N*-benzoyl-β-phenyl isoserine side chain. In this study, a simple precursor of side chain has been synthesized under microwave radiation by the condensation of benzaldehyde, ammonium acetate and malonic acid. The time required for the resulting β-amino acid was remarkably reduced from 6 h to 30 s only along with rapid, easy, simple and safe methodology. The structure elucidation of synthesized compound was done by its melting point, solubility, TLC techniques and spectral analyses.

Key Words: Taxol, Diterpenoid, 10-deacetyl baccatin III, β-Amino acid, Microwave.

Taxol (*Paclitaxel*) is one of the natural diterpenoid alkaloids isolated primarily from the bark of the Western Yew tree (*Taxusbrevifolia*)[1] (Fig. 1).

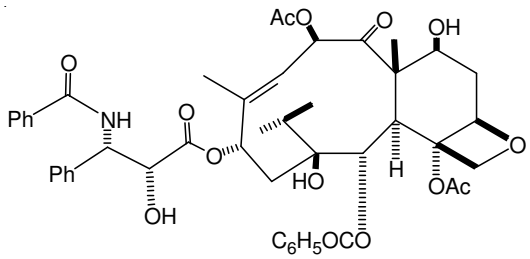


Fig. 1. Structure of Taxol

Because it can kill tumor cell by enhancing the assembly of microtubules and inhibiting depolymerization[2], taxol has been well established and approved by the food and drug administration (FDA) as a very important effective chemotherapeutic agent against a wide range of tumors since[3].

However, the supply of taxol has been limited since the discovery of this natural product and with increasing demands in chemotherapy; the availability and cost of the drug will remain an important issue[4].

However, it has been found that 10-deacetyl baccatin III, the abundant constituent of the needles of the European yew tree species *Taxusbaccata*, is more readily obtained[5].

Several methods have been reported for the semi synthesis of taxol by coupling baccatin III and the side chain of taxol. It is known that C-13 side chain, *i.e*. *N*-benzoyl-(2R, 3S)-3-phenylisoserine (Fig. 2) moiety is crucial for the activity of taxol[6].

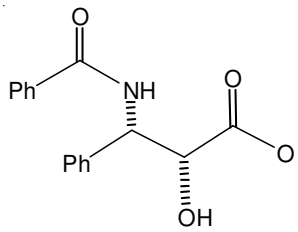


Fig. 2. Structure of taxol side-chain

Semi-synthetic taxol work[7] has generated a demand for new stereoselective synthesis of isoserine type structure. The C-13 contains a complex *N*-benzoyl phenyl isoserine ester group, which is known as the taxol side-chain. The aim of the work is to improve and provides an efficient and rapid method for the synthesis of taxol side-chain.

All chemicals used in the synthesis were of analytical grade from Merck and Fluka. Melting points of synthesized compounds were determined using Gallenkamp melting apparatus. Ultraviolet spectra were recorded within the range 200-500 nm on Hitachi U-2800 spectrophotometer. FTIR

TABLE-1
CONVENTIONAL HEATING VERSUS MICROWAVE RADIATION FOR THE SYNTHESIS OF TAXOL SIDE-CHAIN PRECURSOR

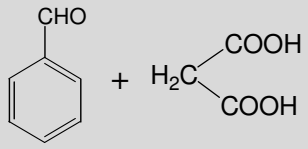
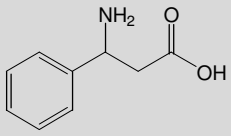
S. No.	Substrate	Product	Conventional heating		Microwave irradiation	
			Time (min)	Yield (%)	Time (sec)	Yield (%)
1.	 Benzaldehyde malonic acid ammonium acetate	 β-Amino acid	360	70	30	80

TABLE-2
FTIR ANALYSIS

S. No.	Compound	Bands (cm^{-1}) and Intensity
1.	3-amino-3-phenyl propanoic acid	Conventional: 3156, 1980 w, 1725 s, 1614 w, 1402 s, 1283 m, 1105 m, 887 w, 664 m. Microwave: 4471 w, 3938 w, 3736 w, 3409 w, 3205 w,b, 2925 w, 2351 w, 1566 s, 1408 s, 1121 m, 714 m, 657 w.

spectra were recorded within the range 4000-400 cm^{-1} as KBr pellets on a Midac M-2000 spectrometer (USA) while mass data were recorded on GC-MS Schimadzo QP-2010 spectrometer (Japan). For the microwave-assisted synthesis of compound, microwave oven DW-180, 2450 MHz, 950 W was used.

Synthesis of 3-phenyl-3-amino-amino acid

Conventional: A mixture of benzaldehyde (2.0 mL), malonic acid (2.08 g), ammonium acetate (3.08 g) in ethanol (30 mL) was refluxed for 6 h. The compound was precipitated from the reaction mixture after cooling. The white solid thus obtained was separated by simple filtration. Yield (70 %), m.p. 220 ºC

Microwave: A mixture of benzaldehyde (1.0 mL), malonic acid (1.04 g), ammonium acetate (1.5 g) in ethanol (15 mL) was irradiated for 30 s. to give β-amino acid, which was washed and dried. Yield (80 %), m.p. 218 ºC

The present study has made an attempt to synthesize side-chain precursor β-amino acid, by both methods *i.e.* conventional and microwave-assisted. It was observed that the time required for the synthesis of 3-amino-3-phenyl propanoic acid (β-amino acid) under microwave radiation was remarkably reduced from 6 h to thirty seconds with better yield as shown in Table-1.

In taxol-side chain precursor the amino group showed medium absorption near 3200 cm^{-1} and carboxyl group gave bending vib. frequency at 1600 cm^{-1} and stretching vib. near 3300 cm^{-1} as given in Table-2.

Mass spectrum of taxol side chain precursor is recorded in Table-3. The base peak which appeared at m/z = 91 shows the presence of benzyliccation $C_6H_5CH_2^+$ while the molecular ion peak at m/z = 136 shows the fragmentation which contain amino group.

TABLE-3
GC-MS OF TAXOL-SIDE CHAIN PRECURSOR

S. No.	Compound	Formula	Base Peak	Molecular ion Peak M^+
1.	Taxol side-chain precursor	$C_9H_{11}NO_2$	91	136

Conclusion

Taxol side-chain precursor has been prepared from cheap and inexpensivestarting materials and reagents by utilizing the application of microwave. The time required for this synthesis was reduced from 6 h to 30 sec only with good yield. So by selecting such a novel method, a large number of medicinally important compounds can be prepared within a short time.

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