Microwave assisted facile synthesis of amino acid benzyl ester p-toluenesulfonate and hydrochloride salts

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Summary
A simple method for the synthesis of several amino acid benzyl ester p-toluenesulfonate salts from the corresponding amino acid and benzyl alcohol in presence of p-toluenesulfonic acid accelerated with microwave irradiation is described. Under similar condition, the amino acid benzyl ester hydrochloride salts have also been obtained by using thionyl chloride instead of p-toluenesulfonic acid in good yield and purity.

Introduction
Microwave-assisted organic synthesis [1–5], introduced independently by Giguere [6] and Gedye [7] groups, is a environmentally friendly procedure for heating materials which is distinctly different from the well tested classical thermal route. Its main advantage [8] is due to the instaneous localized superheating of materials in an homogeneous and selective manner. Further, remarkable decrease in the time necessary to carry out reactions (upto three orders of magnitude), cleaner reactions coupled with easier work-up, selectivity leading to high purity in high yields, etc., are being explored very quickly in developing alternative pathways for the synthesis of organic molecules.

There are few initial reports utilizing the microwave ovens in peptide and protein chemistries during 1989–1992 [9–13]. Both the hydrolysis of proteins into amino acids to determine the amino acid analysis [9,10] and the synthesis of polypeptides like poly(GAMD), poly(GALD), poly(GAVD), poly(GAVDH), etc., [11,12] using the microwave irradiation have been demonstrated. The use of microwave ovens in the solid phase synthesis of acyl carrier protein fragment 65–74 employing Fmoc-amino acids using either symmetrical anhydrides or active esters for coupling with a significant reduction in reaction time (2–6 min.) compared to classical coupling procedures with high yield was also accomplished [13]. Although microwave ovens have already found a place in organic chemistry laboratory, their utility in peptide chemistry is yet to be fully demonstrated. This communication deals with the rapid, simple and efficient synthesis of amino acid benzyl ester p-toluenesulfonate and hydrochloride salts using an unmodified domestic microwave oven.

Materials and methods
The melting points were determined using a Leitz-Wetzlar melting point apparatus and are uncorrected. The optical rotations were measured with an automatic AA-10 polarimeter (Optical Activity, U. K.). The I.R. spectra were recorded using a Nicolet Impact 400D I.R. spectrometer (KBr pellets, 3 cm⁻¹ resolution). ¹H NMR spectra were recorded on a Bruker ACF 400 MHz spectrometer using Me₄Si as an internal standard. A commercial, domestic microwave oven (LG little chef model 194A) operating at 2450 MHz frequency was used in all experiments.
Synthesis of amino acid benzyl ester p-toluenesulfonate salts: General procedure

A mixture of amino acid (10 mmol), benzyl alcohol (3 mL) and p-toluenesulfonic acid (11 mmol) was placed in a 100 mL glass beaker and exposed to microwave irradiation operating at its 40% power. The reaction mixture, after the completion of the reaction, was cooled to room temperature and precipitated with ether (25 mL). The crystalline p-toluenesulfonate salt of amino acid benzyl ester was collected on a filter, washed with ether and dried in air.

Synthesis of amino acid benzyl ester hydrochloride salts: General procedure

A similar procedure used for the synthesis of amino acid benzyl ester p-toluenesulfonate salt as described above was employed for the synthesis hydrochloride salts of amino acid benzyl esters except that instead of p-toluenesulfonic acid an equimolar quantity of freshly distilled thionyl chloride was used. After the precipitation of the hydrochloride salt, the crystalline compounds were washed using ether three to four times in order to ensure the complete removal of traces of thionyl chloride.

Results and discussion

In the present studies, the synthesis of amino acid benzyl ester p-toluenesulfonate and hydrochloride (scheme 1) salts has been accomplished in a facile way utilizing microwave irradiation. The esterification reaction was carried out by exposing the slurry of amino acid, benzyl alcohol and p-toluenesulfonic acid in a beaker to microwaves in an unmodified domestic microwave oven operating at 2450 MHz frequency at its 40% power. The benzyl ester formation, as monitored by TLC (n-butanol : acetic acid : water :: 4 : 1 : 1), is found to be complete in about 40 to 60 seconds. The addition of dry ether to the resulting gum in the same beaker resulted in the precipitation of the benzyl