MICROWAVE-ASSISTED PHOSPHA-MICHAEL ADDITION REACTIONS ON 13α-ESTRANE CORE

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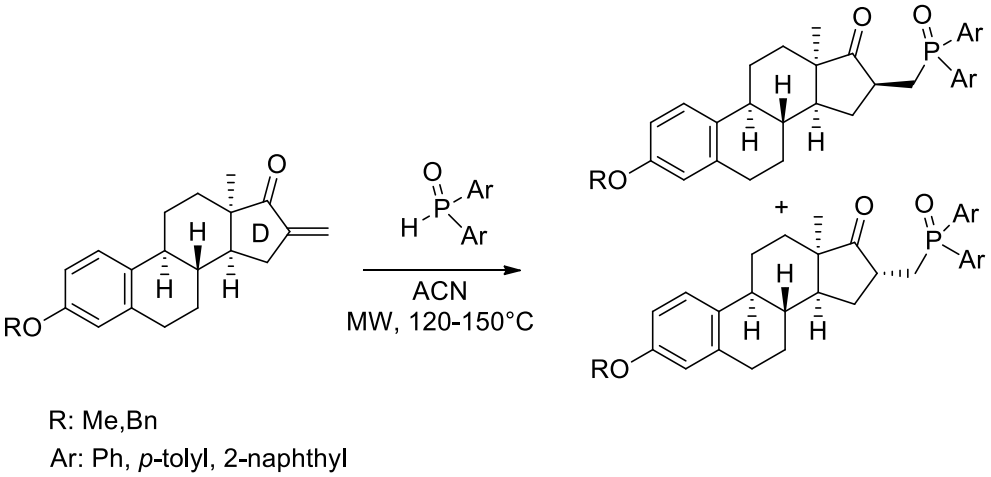
Abstract
Novel 16-modified 13 α-estrone derivatives were synthesized via phospha-Michael addition reactions. Transformations of steroidal α,β-unsaturated ketons were carried out under different conditions in a microwave (MW) reactor. The antiproliferative activities of the newly synthesized compounds against a range of human adherent cancer cell lines (SCC-131, SCC-154, Hela, SiHa, C33A, A2780, MCF-7, MDA-MB-231, T47D) were investigated by means of MTT assays. Certain potent derivatives were identified.

Introduction
Certain substituted estrone derivatives possess anticancer properties. The core-modified 13α-estrone does not possess estrogenic behavior and offers great possibilities concerning selective bioactivities[1]. Certain C-16 modified derivatives display outstanding cell growth-inhibitory action against a range of human adherent cancer cell lines[2]. The microwave assisted phospha-Michael addition of dialkyl phosphites or diarylphosphine oxides to α,β-unsaturated ketones is a known method for the synthesis of organophosphorous compounds[3–5]. It might efficiently be carried out without a catalyst and under short reaction times. Our aim was here to develop a facile and efficient microwave-induced phospha-Michael addition methodology for the synthesis of 16-modified 13 α-estrone derivatives. Investigation of the antiproliferative effect of the newly synthesized 13α-estrone derivatives against a panel of nine human adherent cancer cell lines (SCC-131, SCC-154, Hela, SiHa, C33A, A2780, MCF-7, MDA-MB-231, T47D) was also planned.

Results and discussion
In the first experiments, diphenylphosphine oxide was reacted with the 3-methyl or -benzyl ether of the α,β-unsaturated ketone in acetonitrile, under MW irradiation (Scheme 1). 3-Methyl ether starting compound was completely transformed under 1 h irradiation at 120 °C. In case of the 3-benzyl ether, higher reaction temperature (150 °C) was needed. The reactions of bis(*p*-tolyl)phospine oxide or di(naphthalen-2-yl)phospine oxide as reagents were carried out under the conditions applied for the transformations of benzyl ethers. All the reactions furnished the desired products (in a 2:1 diastereomeric ratio) in high yields. The diastereomers could efficiently be separated by flash chromatography. The structures of the new compounds were confirmed by ^{1}H and ^{13}C and ^{31}P NMR measurements. Certain newly synthesized products displayed substantial antiproliferative action against human adherent cancer cell lines.



R: Me,Bn
Ar: Ph, *p*-tolyl, 2-naphthyl

Scheme 1. Phospha-Michael additions in the 13 α-estrone series

Conclusion

In conclusion, we have developed an efficient microwave-assisted phospha-Michael addition method for the synthesis of steroidal phosphine oxides. 12 new ring D modified 13α-estrone derivatives have been synthesized. Potent antiproliferative compounds have been identified.

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