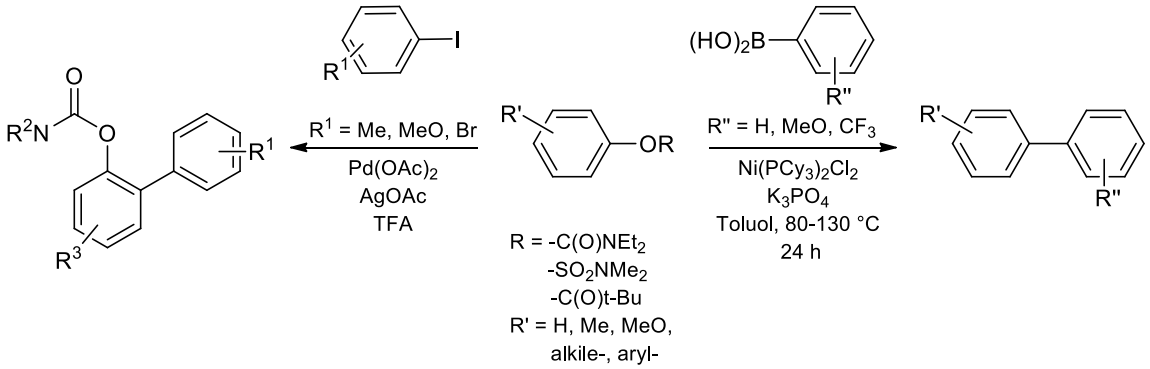
TRANSITION METAL-CATALYZED SYNTHESIS OF 13α-ESTRONE DERIVATIVES WITH POTENTIAL ANTICANCER PROPERTIES

Péter Traj,[1] Ali Hazhmat Abdolkhaliq,[2] Anett Németh,[1] Sámuel Trisztán Dajcs,[1] István Zupkó,[2] Erzsébet Mernyák[1]

Department of Organic Chemistry, University of Szeged, H-6720 Szeged, Dóm tér 8, Hungary[2]
Department of Pharmacodynamics and Biopharmacy, University of Szeged, Eötvös u. 6., H-6720 Szeged, Hungary
e-mail: trajpeter@chem.u-szeged.hu

Abstract
Synthesis of 3-(*N*,*N*-dimethylcarbamoyl)-13α-estrone and its 17-deoxy counterpart has been carried out. The dimethylcarbamoyl directing group enabled the regioselective ortho arylation of the steroidal starting compounds. The microwave-assisted, palladium-catalyzed phenylations led to 2-substituted 13α-estrones in a one-pot, tandem process. The Suzuki-Miyaura cross coupling reactions of the carbamates with phenylboronic acid resulted in 3-phenyl-3-deoxy-13α-estrone. Certain newly synthesized compounds displayed potent antiproliferative action against human reproductive cancer cell lines of gynecological origin.

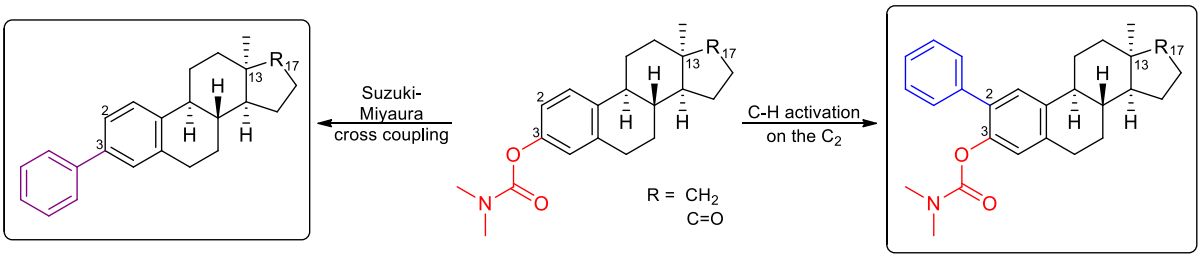
Introduction
At the beginning of 2000s, the synthetic chemistry has completely changed. In recent years more attention is paid to the principles of green chemistry. Application of halogen-free reagents, effective energy transfer methods and fast catalytic circles displaced the traditional preparative chemical processes. That is why transition metal-catalyzed cross-coupling reactions are becoming increasingly popular [1-4]. These new methods facilitate reactions with higher nuclear efficiency, which were previously available with much lower yields. The combination of transition metal-catalysis with microwave irradiation is a promising approach in the modern synthetic organic chemistry. The major advantages of the microwave irradiation methods are: higher selectivities, lower reaction temperatures and shorter reaction times. Concerning the transition metal-catalyzed cross coupling reactions, phenol esters are increasingly used as electrophile partners instead of aryl halides [5-7]. Phenol esters are of great importance even in the C-H activation processes, depending on the nature of the directing group [8] (Scheme 1.).



Scheme 1.: Cross coupling and C-H activation reactions of phenol esters.

Aims

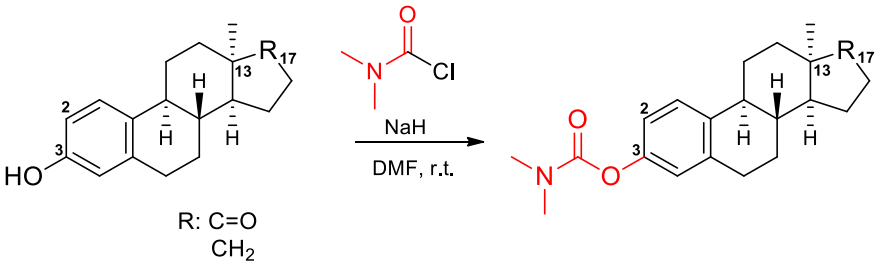
The introduction of the *N*,*N*-dimethylcarbamoyl group on the phenolic hydroxy function of 13α-estrone and its 17-deoxy derivative was planned. Transition metal-catalyzed reactions of carbamates were aimed in order to synthesize 2- or 3-phenyl 13α-estrone derivatives. The newly introduced function might serve as a leaving or a directing group in the transformations (Scheme 2.). The determination of the antiproliferative properties of the newly synthesized derivatives against human adherent cancer cell lines was also planned.



Scheme 2.: Carbamoyl group as a good leaving and directing group in transition metal-catalyzed reactions.

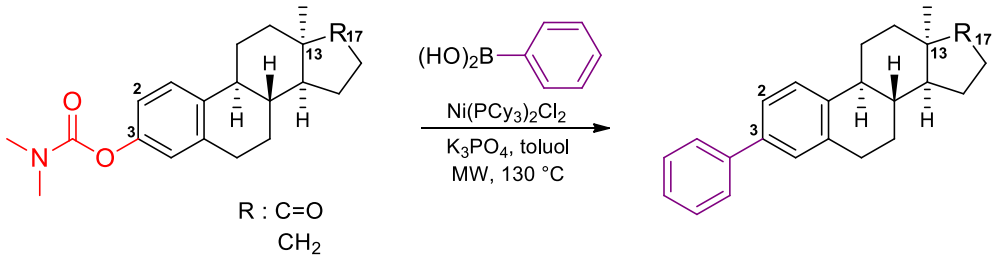
Results and discussion

Firstly, carbamates were synthesized, using *N*,*N*-dimethylcarbamoyl-chloride as a reagent and sodium hydride as a base (Scheme 3.). The reactions were performed at room temperature and the products were isolated with high yields.



Scheme 3.: Synthesis of the carbamates

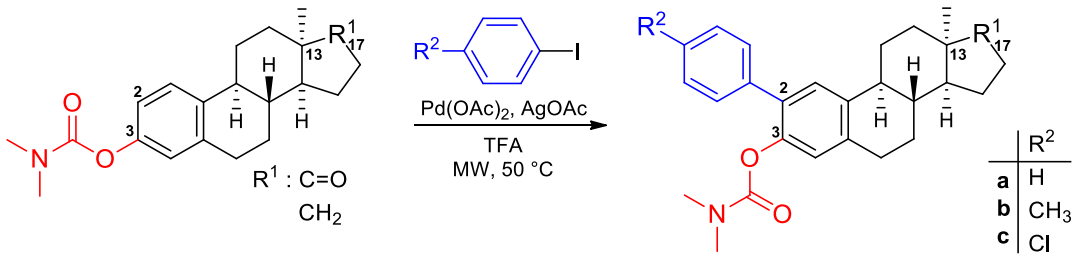
As a next step, carbamates were used in Suzuki-Miyaura cross coupling reactions as starting compounds (Scheme 4.). $NiCl_2(PCy_3)_2$ was chosen as a selective and environmentally friendly catalyst. The microwave-assisted couplings of the steroidal carbamates with phenylboronic acid as a reagent furnished the desired 3-phenyl-3-deoxy derivatives in moderate yields.



Scheme 4.: Suzuki-Miyaura cross couplings in the 13α-estrone series

As a continuation of our work, the steroidal carbamates were subjected to palladium-catalyzed C-H activation reactions (Scheme 5.). 4-Iodobenzene, 1-iodo-4-methylbenzene and 1-chloro-

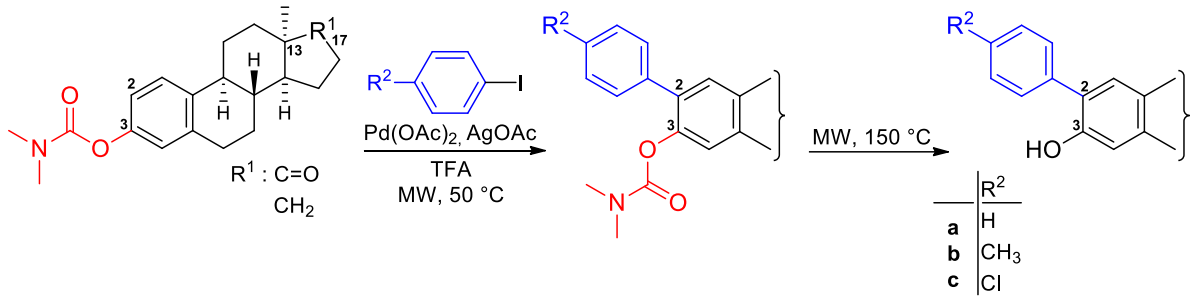
4-iodobenzene were chosen as reagents. The reactions were performed in the presence of silver-acetate and trifluoroacetic acid. Application of microwave irradiation led to the formation of the desired products in high yields. Due to the presence of the directing group, ortho substitution occured exclusively at the C-2. Substitution at C-4 was not observed, probably due to the steric hindrance of the B-ring.



Scheme 5.: C-H activation at the ortho position

The C-H activation and the removal of the directing group could be performed in one step by varying the conditions of microwave irradiation. (Scheme 6.). Literature reveals that the removal of the directing group should be carried out in a further reaction step, thus reducing the efficiency of the process. Our microwave-assisted process allows the introduction of the phenyl group and the cleavage of the directing group in a one-pot, tandem reaction.

The antitumoral properties of the novel 13α-estrone derivatives against a panel of human adherent breast (MCF-7 and MDA-MB-231), cervical (HeLa and SiHa), and ovarian (A2780) cancer cell lines were determined by means of MTT assay. Structure-activity investigations reveal that the antiproliferative action greatly depends of the substitution pattern or A-ring. Certain compounds displayed substantial cell growth-inhibitory actions. The ortho-phenylation overally improved the activity of the 3-modified derivatives.



Scheme 6.: Phenylation at C-2 and cleavage of the directing group

Conclusion

In summary, steroid carbamates have been prepared from 13α-estrone and its 17-deoxy derivative. Carbamates proved to be suitable for nickel- and palladium-catalyzed phenylations at C-2 or C-3. Steroidal phenol esters are “greener” alternatives to steroidal aryl halides in cross coupling reactions. We have developed an efficient, microwave-induced, one-pot, tandem C-H activation and deprotection method for the synthesis of biphenyl derivatives starting from phenol carbamates.

Acknowledgements

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