DEVELOPMENT OF MULTI-GRAM SCALE MICROWAVE ASSISTED ORGANIC SYNTHESIS (MAOS): SUZUKI COUPLING TOWARDS 2,4-DIMETHYL-8-[2'-(2H-TETRAZOL-5-YL)-BIPHENYL-4-YLMETHYL]-5,8-DIHYDRO-6H-PYRIDO[2,3-D]PYRIMIDIN-7-ONE (TASOSARTAN)

Klaus Gerdes[a], Ulrich Jordis[a], C. Oliver Kappe[b] and Jennifer M. Kremsner[b]

[a] Institute of Applied Synthetic Chemistry, Vienna University of Technology
Getreidemarkt 9, 1060 Vienna, Austria, ujordis@pop.tuwien.ac.at

[b]*Institute of Chemistry, Karl Franzens Universität Graz, Heinrichstrasse 28, 8010 Graz*

Abstract. The improved synthesis of 2,4-dimethyl-8-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-5,8-dihydro-6H-pyrido[2,3-d] pyrimidin-7-one (tasosartan-1, click for 3D-structure) on multigramscale is described. The synthesis was developed in context of the DrugMatrix-genomics project.

Keywords. Angiotensine II antagonist, Suzuki-coupling, microwave

Introduction. The improved synthesis of 2,4-dimethyl-8-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-5,8-dihydro-6H-pyrido[2,3-d] pyrimidin-7-one (tasosartan 1) on multigram-scale is described. Tasosartan is an angiotensin II antagonist and was used for treatment of hypertension. Due to unresolved safety issues its NDA application was withdrawn in 1998. However, Tasosartan and its metabolites are still of interest in genomic and pharmaceutical studies [1, 2]. Here the synthesis was developed in context of the DrugMatrix [3] genomics project.

Results and discussion. 2,4-Dimethyl-8-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (Tasosartan) **1** was synthesized according to literature known procedures [4, 5] starting from 4-bromobenzylamine hydrochloride **2** and benzonitrile **3** in a convergent strategy. The key-step of the synthesis was the palladium catalysed Suzuki-coupling of boronic acid **4** and bromide **5**. For this reaction investigations on small scale in microwave oven compared to conventional heating under various conditions were carried out, as well as a protocol for upscaling under microwave conditions was developed.

Scheme: Convergent preparation of Tasosartan 1

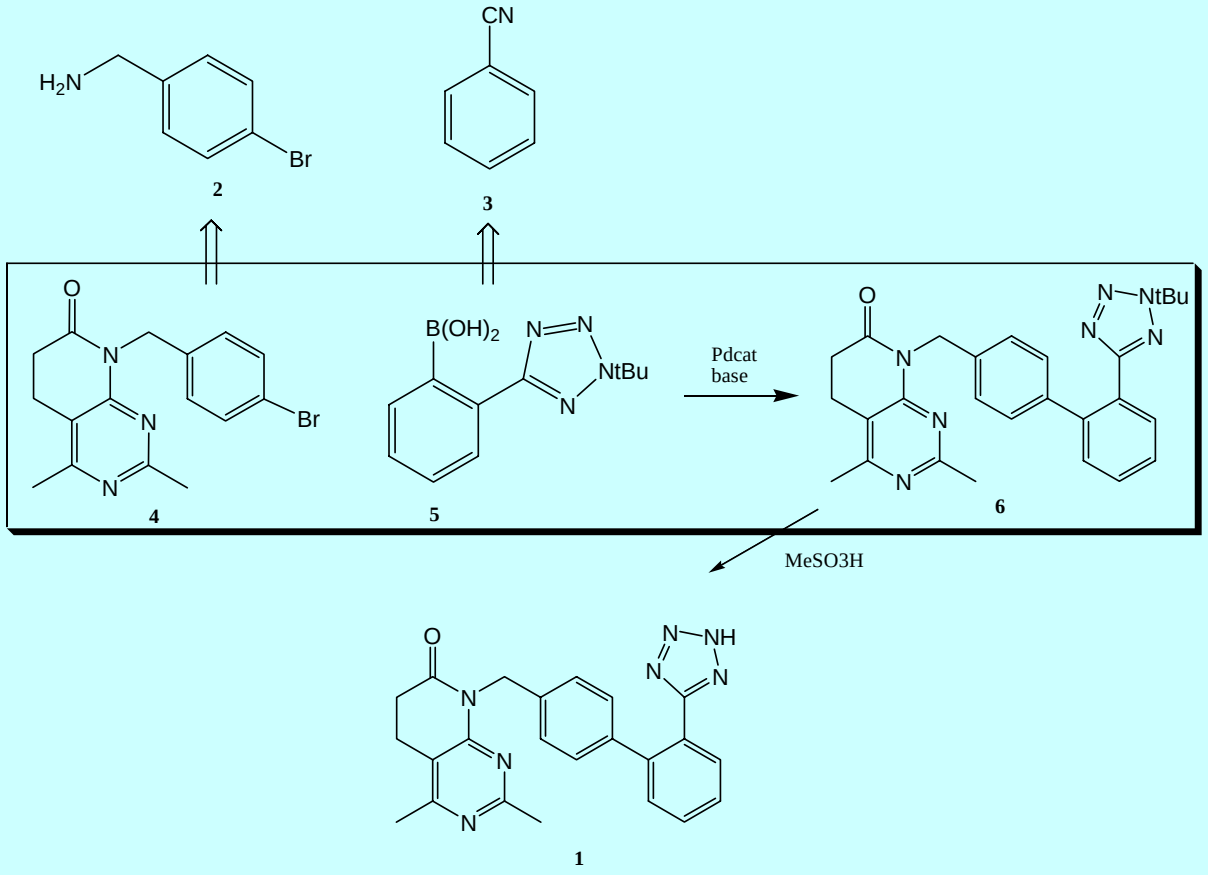

Table 1: Details for the conditions used in the Suzuki-coupling

TIME. [h]/TEMP. [°C]	BASE	SOLVENT	CATALYST (4-MOL%)	SCALE	HPLC-YIELD OF 6 (%)	HEATING
16/110	K_2CO_3 (2M)	Tol./EtOH10:1	$Pd[P(Ph_3)]_4$	14	55	conventional
48/110	K_2CO_3 (2M)	Tol/EtOH 10:1	$Pd[P(Ph_3)]_4$	31	33	conventional
0.5/120	K_2CO_3 (2M)	Tol/EtOH 5:1	$Pd[P(Ph_3)]_4$	0.7	52	µW
0.5/140	K_2CO_3 (4M)	Tol/EtOH 5:1	$Pd[P(Ph_3)]_4$	0.7	63	µW
0.5/140	K_2CO_3 (4M)+ BTBA*	Tol/EtOH 5:1	$Pd[P(Ph_3)]_4$	0.7	51	µW
0.5/150	KOtBu	DMF	$Pd[P(Ph_3)]_4$	0.7	69	µW

0.5/140	K_2CO_3	DMF	Pd/C	0.7	traces	µW
0.5/140	K_2CO_3 (4M)	Tol/EtOH 5:1	C_{28} H_{37} Cl N P Pd**	0.7	38	µW
0.5/140	**K_2CO_3 (4)**	**Tol/EtOH 5:1**	**$Pd[P(Ph_3)]_4$**	**0.7**	**84**	µW
1/140	**K_2CO_3 (4)**	**Tol/EtOH 5:1**	**$Pd[P(Ph_3)]_4$**	**70**	**71**	µW

* Benzyltributylammonium; **Palladium, [bis(bicyclo[2.2.1]hept-2-yl)phosphine]chloro[2'-(dimethylamino-kN)[1,1'-biphenyl]-2-yl-kC]- (9CI)

Table 1 shows the results of the palladium catalysed Suzuki-coupling of bromide 4 and boronic acid 5 under various conditions. For the upscaling of the reaction under conventional heating a dramatically drop in the yield of the desired product to 33% only was observed (entry 2). Therefore investigations on small scale MAOS [6] were carried out to find an optimal procedure to transfer it to multigram scale MAOS. It was of advantage to use higher concentrated aqueous K2CO3 solution were as use of phase-transfer-catalyst or KOtBu showed no major improvement (entries 5 and 6). Also the application of different catalyst-systems (entries 7 and 8) did not give improved results. Best results could be achieved with Pd[P(Ph)3]4 (4mol%) as catalyst, 4M K2CO3 and Toluene/EtOH 5:1 as solvent mixture (entry 9). This protocol was then transferred to large scale MAOS by using Anton Paar reactor Synthos 3000 on a 70 mmol scale to yield the desired coupling product in good yield.

Anton Paar	Anton Paar Synthos 3000 www.anton-paar.com

Conclusion: In summary, we have developed an efficient and high yielding route towards the preparation of tasosartan applying small- and large scale MAOS in up to 70 mmol.

References.

[1] Jack D. Drug News and perspectives, 2000, 13, 121-124;
[2] Maillard M. P., Rossat J., Brunner H. R., Burnier R., Journal of Pharmacology and Experimantal Therapeutics, 2000, 295, 649-654.
[3] http://www.iconicpharm.com/products/products_main.html
[4] Ellingboe J. W., Antane M., Ngyen T. T., Collini M. D., Antane S., Bender R., Hartupee D., J. Med. Chem., 1994, 37, 542-550;
[5] Ellingboe J. W., Nikaido M., Bagli J. F., EP, 539086, 1993;.
[6] For a recent review see: Kappe C.O., Angew. Chem. Int. Ed. 2004, 43, 6250-6284