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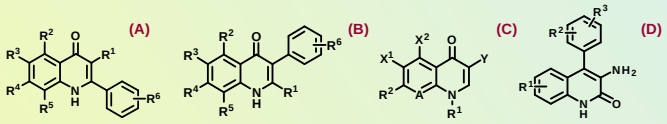
Microwave Assisted Synthesis of Substituted 2(1H)-Quinolones as Maxi-K⁺ Channel Openers

Toma Glasnov, Wolfgang Stadlbauer and C. Oliver Kappe*

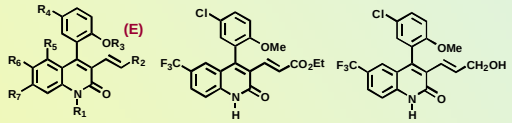
Institute of Chemistry, Dept. Of Organic and Bioorganic Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria
Fax: +43-316-3809840; E-mail: toma.glasnov@uni-graz.at, oliver.kappe@uni-graz.at; http://www.maos.net

❶ Introduction

The quinolone moiety and its derivatives are known to possess a wide range of biological activity. For different substituted arylquinolones anticancer[1] **(A,B)**, antimicrobial[2] **(C)**, and neuroprotective[3] **(D)** properties have been found.



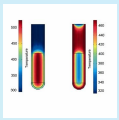
Recently it was found that certain 3-substituted 4-arylquinolones **(E)** are potential Maxi-K⁺ channel openers.[4] According to the classification of possible treatments for male erectile dysfunction (ED)[5], affecting the Maxi-K⁺ channels is a promising way for effective currance of the persistant inability of a man to achieve and/or maintain erection.



[1] a) Lee et al., *US Patent 5571822*, **1996**; b) Beney et al., *Tetrahedron Lett.* **2000**, *41*, 7037-7039; c) Joseph, B. et al., *J. Med. Chem.* **2002**, *45*, 2543-2555; d) Joseph, B. et al., *Synlett* **2003**, *10*, 1541-1544; e) Traxler, P. et al., *J. Med. Chem.* **1999**, *42*, 1018-1026; [2] BAYER AG *EU Patent 0343 398*, **1989;** [3] Hewawasam, P. et al., *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1779-1783; [4] a) BMS *Patent WO 00/34244*, **2000;** b) Hewawasam, P. et al., *J. Med. Chem.* **2003**, *46*, 2819-2822; c) Wang, J. et al., *Tetrahedron Lett.* **2003**, *44*, 4271-4273; [5] Andersson, K.-E., *Pharmacol.Rev.* **2001**, 53, 417-450;

❷ Organic Synthesis in Microwave Reactors

When using traditional heating under reflux conditions many C-C and C-X bond forming reactions typically need hours or days to reach completion. Therefore fast and reliable microwave protocols have to be created, taking into account the advantages of microwave heating – rapid transfer of energy and inverted temperature gradients, which eliminates e.g. wall effects seen in conventional heating methods[6].

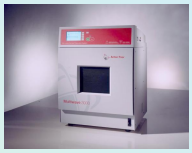


Optimization of the microwave synthesis was performed in a single-mode reactor (sealed vessels) with possibilities for automated dispensing of reaction components and automated vessel transfer. For scale-up a multimode-cavity reactor was used directly applying the conditions obtained in the small-scale runs.

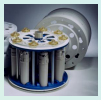
Emrys™ Synthesizer

+ sample robot
+ up to 120 reactions
+ magnetic stirring
+ 12-15 reactions/hour
+ 0-300 W
+ 60-250 °C, 0-20 bar

Anton Paar Synthos 3000™



+ 80 ml quartz vessels
+ 8 or 16 vessel rotors
+ magnetic stirring
+ 0-1400 W
+ 60-300 °C, 0-80 bar



[6] a) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717; b) Kappe, C.O. *Angew. Chem. Int. Ed.* **2004**,*43*, *in press*

❸ Novel Microwave Supported Reaction Sequence

Here we present a novel synthetic strategy for synthesis of 4-aryl-2(1H)-quinolone lead compounds for the treatment of male ED. The MW-reaction protocols are high-diversity generating, flexible, amenable to high-speed MAOS, scalable and involve commercially available building blocks. Our approach for making the 4-arylquinolones includes a cyclization step, chlorination/hydrolysis, Suzuki C-C coupling,[8] bromination, and finally a Heck reaction, **all under microwave conditions**.[9] Having optimized the sequence on mg scale a succesfull MW-scale-up to gram quantities with comparable yields was performed.

● The first steps

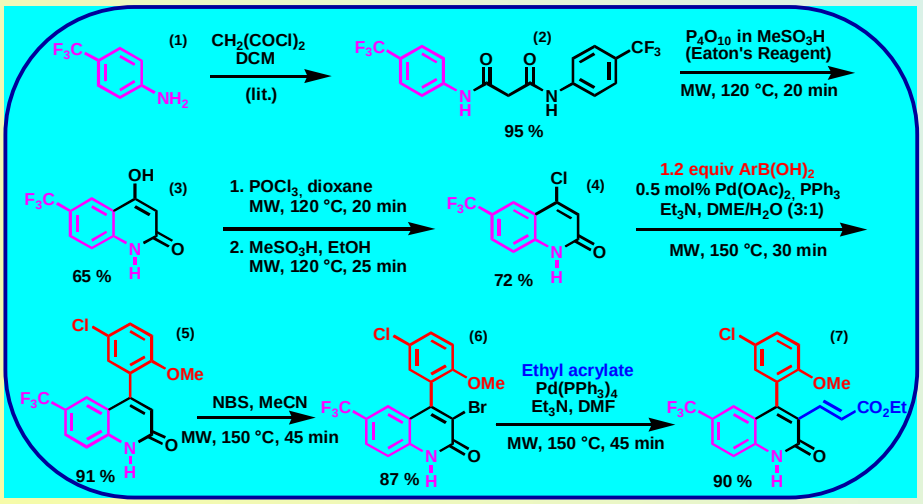
✓ commercially available starting materials: anilines and malonylchloride;

✓ simple literature procedure[7] giving dianilide **(2)** in 95% yield;

✓ MW – optimized cyclisation protocol for the synthesis of 4-hydroxy-(2*H*)-quinolone **(3)**;

● Preparing for Suzuki

✓chlorination - hydrolysis sequence in MW to obtain 4-chloro-(2*H*)-quinolone **(4)**;



● Suzuki C-C coupling reaction

✓rapid MW procedure for Suzuki arylation leading to 4-aryl-2-quinolones;

✓ optimization of solvent, catalyst, base, temperature and time needed for the reaction to proceed

✓ 91% of HPLC-pure product **(5)** in a simple work-up.

● Bromination

✓ fast MW – protocol
✓conversion of 87%.

● The Heck vinylation

✓electron-rich heteroaromatic chloride for Suzuki C-C coupling, obtained in 72% yield;

✓ Heck vinylation as last step, leading to the desired poduct **(7);**
✓ simple MW-procedure with **standard Pd(0)** catalyst
✓ reaction time and purification in 1h;

[7] Bertolini, G. et al., *J. Med. Chem.* **1997**, *40*, 2011-2016; [8] For reviews see a) Littke, A., Fu, G.C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176-4211; Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168; c) Miyaura, N., *"Advances in Metal-Organic Chemistry"* **1998**, *6*, 187 -243; d) Suzuki, A. *„Metal-Catalyzed Cross-Coupling Reactions"*, Wiley-VCH, New York, **1998**, chap. 2; e) Stanforth, S. P., *Tetrahedron* **1998**, *54*, 263-303; f) Miyaura, N. Suzuki, A., *Chem. Rev.* **1995**, 95, 2457-2483.; Others: a) Larhed, M., Hallberg, A., *J. Org. Chem.* **1996,** 61, 9582-9584; b)Tagata, T., Nishida, M. J. Org. Chem. **2003**, *68*, 9412- 9415; c) Leadbeater, N., Marco, M., *J. Org. Chem.* **2003**, *68*, 888-892; [9] Littke, A., Fu, G. C., *Angew. Chem. Int. Ed.* **2002**, *41*, 4176-4211 and references therein.

❹ Conclusion

Synthesis route:

× novel strategy, all steps using MW
× no purification necessary, only final compound is purified
× 38% overall yield (7 steps)

Advantages of Microwave Synthesis:

× dramatic rate-enhancements for e.g. transition metal-catalyzed reactions
× higher yields, cleaner reaction profiles
× better reproducibility

Acknowledgement:

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For further information see: Glasnov, T.N., Stadlbauer, W., Kappe, C.O. J. Org. Cem. 2005, 70, 3864