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[E003] Microwave-assisted synthesis facilitating obtaining of structurally diverse styrylquinolines.

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Introduction

Quinoline is an important heterocycle included in the various classes of pharmacological agents that can play important role in biochemical processes. Possibilities of fictionalization of quinoline moiety made this group of chemicals especially interesting for explore. Known class of biologically active compounds flourish recently are styrylquinolines (SQL). They shown novel therapeutic activities against HIV integrase [1-3] and FZ41 is styrylquinoline compound under preclinical development [4]. SQL's are also studied as antifungal or herbicidal agents. Several methods are available for the synthesis of styrylquinolines. However, they are low yielding and time consuming. Furthermore due to side-reactions and large volumes of organic solvents these protocols produce significant quantities of chemical wastes. Methods for the direct introduction of alkyl substituent into quinoline nuclei depend on reactions of parent heterocycles or their N-oxides with organometallic compounds [5, 6], reaction of chloro-derivatives with active methylene compound salts [7, 8], or with Wittig reagents [9].

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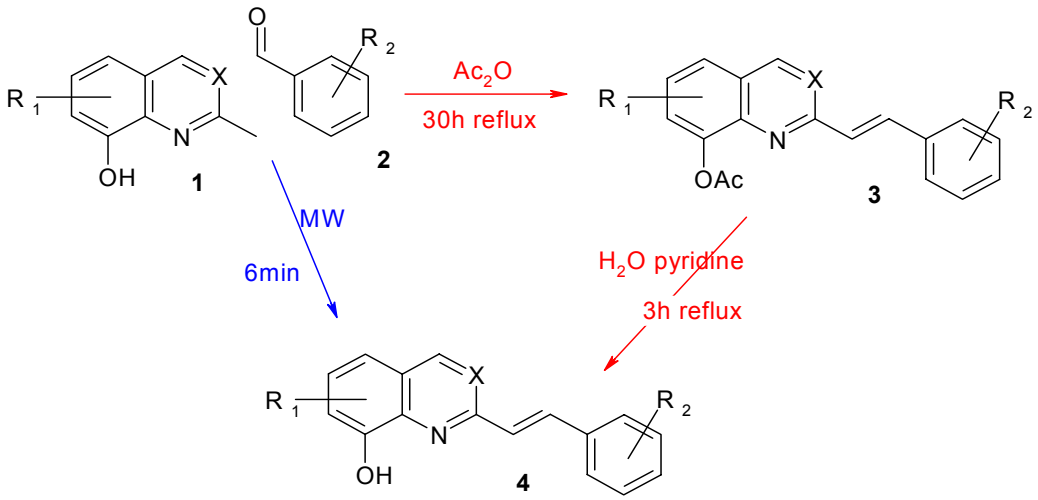
Probably the most convenient described method consists in the reaction of appropriate quinaldine with aldehydes in acetic anhydride (Scheme 1). This requires, however, long time and the excess of reagents that is to be used and results in a reaction mixture which is difficult to purify [10].

During our study on styrylquinoline analogues and their biological activity we came to the conclusion that new rapid and efficient route for structurally diverse styrylquinolines is needed [14, 15].

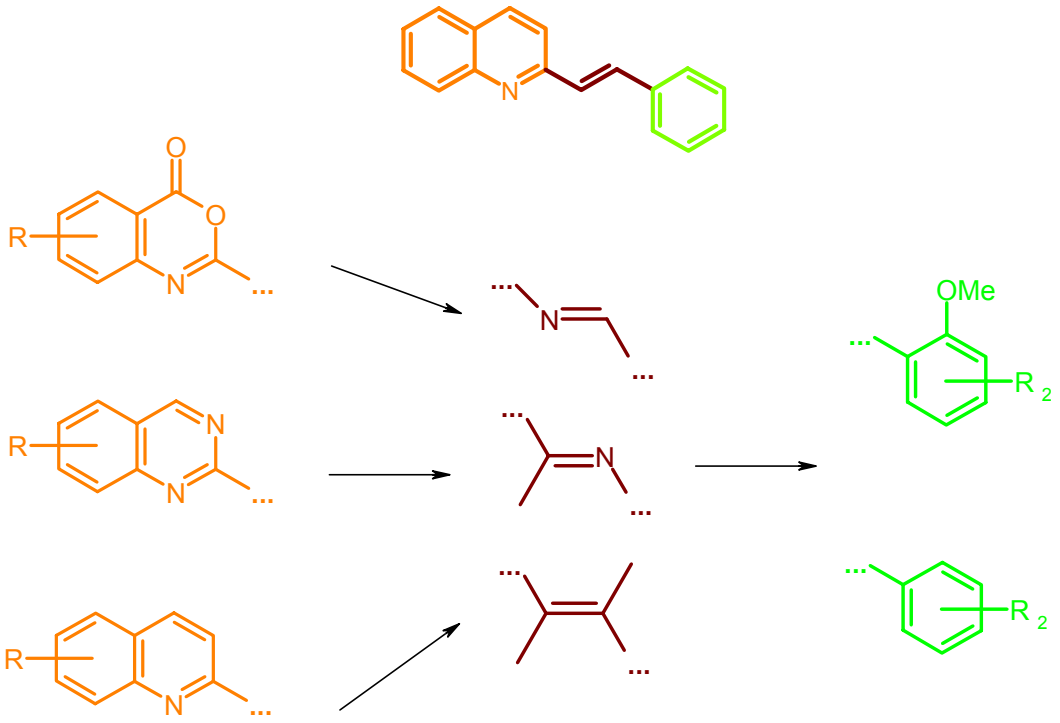
Microwave assisted organic synthesis (MAOS) is an attractive alternative for traditional organic synthesis [11-13]. Especially, the use of surface active catalysts in dry media (also called solvent–free conditions) is highly interesting because of mild conditions and good selectivity. Neat synthesis is another interesting technique in MAOS. This facilitates accomplishing the desired product with minimal amounts of by-products and almost without solvents.



Scheme 1. A comparison of the traditional two-step method and MAOS styrylquinoline syntheses. X=C, N; R_1=COOH, OH, NO_2, NHAc; R_2=OH, OMe, Cl, Br,

After optimization we have facilitated condensation of quinaldines with aromatic aldehydes applying microwave irradiation as a heat source (scheme 1). According this known route to styrylquinolines has been

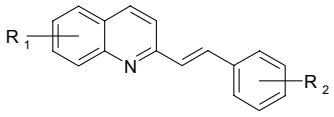
significantly improved and further studies on wide library of styrylquinolines and their analogues have become available (Scheme 2).



Scheme 2. Virtual combinatorial library of styrylquinolines and their analogues. R=COOH, OH, NO_2, NHAc; R_2=Cl, Br, OH, OMe

Experimental

All reactions were performed in open glass tubes according to two protocols. As source of microwave field we used unmodified household ovens (Whirlpool; AVM557 and Electrolux; EMS2820) and microwave reactor designed to laboratory use (Plazmatronika; RM 800PC).Several results are presented in table I, more descriptive group of synthesized compounds will be presented elsewhere [16].

No			Mp [°C]	Yield [%]
	R_1	R_2		
1	6-COOH	2-Cl	256	72
2	7-COOH	4-OMe	268-270	65
3	5-COOH	2,4-OMe	252-260	54
4	5-COOH	4-OMe	253-255	60
5	8-COOH	4-OMe	188-190	82
6	5,8-COOH	2-OH	340-345	68
7	7-COOH-8-OH	4-Cl	178-180	53

Microwave assisted protocols

Neat procedure consists in mixing of appropriate quinaldine with 2 equiv of aldehyde, and exposure the mixture in test tube on microwave irradiation for 6 minutes. Product was then purified by washing with diethyl ether and crystallization [16].

Solid phase procedure involved mixing of the reagents with Al_2O_3 and irradiated at 850W [14]. The resulted product was extracted with appropriate solvent and recrystallized.

Conventional procedure

Procedure utilizing conventional source of heat consist in mixing thoroughly 10mmol of appropriate quinaldine derivative with 6 equiv of aldehyde and heating under inert gas atmosphere during 4 hours. The mixture was then cooled down, washes with diethyl ether and crystallized or chromatographed to afford pure product [2, 15].

Results and discussion

The comparisons of the MW-accelerated reactions and conventional method have been made by conducting the same reaction in an oil bath at the same bulk temperature, under inert gas atmosphere. Due to longer

time of heating required to achieve satisfactory yield, the side reactions were significant under conventional conditions. This had effect on purity of isolated product and solvent usage. Moreover, a traditional two step synthesis can be now performed as a single step process.

Thus the procedure is significantly improved under MAOS condition. The products obtained under such conditions can be purified much easier. It is worth mentioning that a neat synthesis with conventional heating, if tested, did not provide products in high yields. Further this needs complex purification and produce more wastes. Table II shows volumes solvent required to obtain 0,01 M of pure product, including both reaction and crystallization.

Method / Solvents	Conventional heat source [ml]		MAOS [ml]
	acetic anhydride	Neat	
Acetic anhydride	5	–	–
Pyridine	7	–	–
Diethyl ether	50	40	20
EtOH	50	50	50
Dichloromethane	20	–	–

Table II. Approximate amounts of different solvents required to obtain 0,01 mole of pure product.

In conclusion, microwave assisted method of synthesis of styrylquinolines provides a simple and environmentally friendly alternative for the known procedures. MAOS synthesis is not only faster but also improves the yields. As general procedure involves simple mixing of neat reactants the problems associated with waste disposal of reagent excess and solvents can be easily minimized by applying this procedure.

1. ^{1}H NMR (DMSO-d_6, 500MHz) δ: 6.91 (t, *J*=8.0Hz, 1H); 6.97 (d, *J*=7.4Hz, 1H); 7.6 (d, *J*=16.5Hz, 1H); 7.7-7.75 (m, 2H); 7.8 (t, *J*=7.9Hz 1H), 8.08-8.12 (m, 2H), 9.32 (d, *J*=9.5Hz, 1H); 8.58 (d, *J*=7.4Hz, 1H); 8.68 (d, *J*=8.75Hz, 1H).
A.E. found: C=69.56%, H=3.79% calcd.: C=69.8%, H=3.9%

2. ^{1}H NMR (DMSO-d_6, 300MHz) δ 3.82(s, 3H), 7.02(d, *J*=8.7Hz, 2H), 7.37(d, *J*=16.3Hz, 1H), 7.72(d, *J*=8.7Hz, 2H), 7.88(d, *J*=16.3Hz, 1H), 7.98-8.07(m, 3H), 8.45(d, *J*=8.7Hz, 1H), 8.55(s, 1H).
A.E. found:C=70.71%, H=5.28% calcd.: *H_2O C=70.58%, H=5.30%

3. ^{1}H NMR (DMSO-d_6, 500MHz) δ: 3.84 (s, 3H), 3.95 (s, 3H), 6.67 (s, 1H), 7.64-7.79 (m, 3H), 7.94-8.07 (m, 2H), 8.22 (d, *J*=16.1 Hz, 1H), 8.3-8.52 (m, 2H), 9.53-9.62 (m, 1H).
A.E. found:C=68.17%, H=5.64% calcd.: *H_2O C=67.98%, H=5.42%

4. ^{1}H NMR (DMSO-d_6, 500MHz) δ 3.8 (s, 3H); 7.0 (d, *J*=8.7Hz, 2H); 7.35 (d, *J*=16.5Hz, 1H); 7.72 (d, *J*=8.7Hz, 2H); 7.8-7.86 (m, 2H); 7.95 (d, *J*=9.3Hz, 1H); 8.1-8.2 (m, 2H); 9.2 (d, *J*=9Hz, 1H); 13.2 bs.
A.E. found:C=70.45%, H=5.30% calcd.: *H_2O C=70.58%, H=5.30%

5. ^{1}H NMR (DMSO-d_6, 300MHz) δ 3.34 (s, 3H), 7.5(d, *J*=8.5 Hz, 2H), 7.82-7.85 (m, 3H), 8.17 (d, *J*=8.5 Hz, 1H), 8.24 (d, *J*=7.7Hz, 1H) 8.56 (d, *J*=7.6 Hz, 1H), 9.4 (d, *J*=9.1 Hz, 1H).
A.E. found:C=72.33%, H=4.87% calcd.: *1/2H_2O C=72.60%, H=5.13%

6. ^{1}H NMR (DMSO-d_6, 300MHz) δ 6.88-6.98 (m, 2H), 7.26 (t, *J*=8.4 Hz, 1H), 7.58 (d, *J*=16.4Hz, 1H), 7.76 (d, *J*=7.7Hz, 1H), 8.06-8.17(m, 2H), 8.28 (d, *J*=7.7Hz, 1H), 8.57 (d, *J*=7.7Hz, 1H).
A.E. found:C=68.11%, H=4.05% calcd.: C=68.06%, H=3.91%

7. ^{1}H NMR (DMSO-d_6, 500MHz) δ: 7.0 (d, *J*=8.6 Hz, 1H), 7.48 (d, *J*=7.9Hz, 2H), 7.53 (d, *J*=8.2Hz, 1H), 7.6 (d, *J*=16.3Hz, 1H); 7.73 (d, *J*=8Hz, 1H); 78 (d, *J*=8.57 Hz, 1H); 7.88-7.92 (m, 3H); 8.04 (d, *J*=8.6 Hz, 1H), 8.4 (d, *J*=8.5 Hz, 1H).
A.E. found:C=72.06%, H=3.74% calcd.: *H_2O C=71.89%, H=4.10%

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