Optimization of solid phase synthesis of quinazolin-4-ones

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Abstract

Optimization of microwave assisted solid phase synthesis of quinazolin-4-ones was discussed in this paper. Two step synthesis yielded in 2-methyl-4*H*-3,1-beznoxazin-4-one and quinazolin-4-one was optimized in microwave conditions. Different solid supports as well as reaction time, amount of support and temperature were optimized by means of design of experiment approach. We were able to obtain the product with 80% overall yield and with good purity above 95% Resulted terms of synthesis were applied in synthesis of biologically active styrylquinazolines.

Keywords: Solid phase; microwave synthesis; quinazolinones.

Introduction

Chemistry of quinazolines has been explored from the twilight of the 19 century [1]. Nowadays this scaffold still remains important privileged building block for many biochemical studies. Derivatives of quinazolin-4-one were extensively studied as antitumor [2] and antimalarial agents [3]. However, spectrum of biological activity of these compounds is much wider and includes also anticonvulsant [4], analgesic [5], stimulant and antidepressant [6] as well as antibacterial activities [7].

Multistep synthesis from anthranilic acid is probably the widest used method for obtaining quinazolinone moiety. This approach, through 2-methyl-4*H*-3,1-beznoxazin-4-one (Scheme 1, **II**) and, substitution with ammonia or ammonium derivative, offers quite simple and convenient method for obtaining 2-methylquinazolin-4(3H)-one (**III**) with moderate overall yields. On the other hand this method is time consuming and requires considerable excess of solvents or reagents. Thus optimization of synthesis of this scaffold has been extensively studied. Nouira et al. reported microwave assisted synthesis of 2-alkilquinazolines starting from anthranilic acid [8]. Parallel syntheses of combinatorial libraries of quinazoline derivatives via 2-step-one pot reaction [9] and via iron catalyzed reaction [10] were published. Cooper halides were also studied as catalysts for ring closure synthesis of quinazolinones [11]. While former studies were surveyed in excellent review written by Connoly *et* all [12].

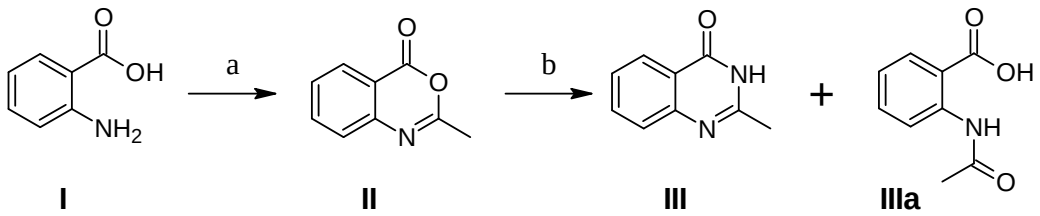
This ceaseless attention of quinazoline chemistry prompts us to present our findings on optimization of the synthesis of 2-methylquinazolin-4(3H)-one in solid phase microwave assisted conditions. We have optimized the classical two steps method with help of the design of

experiment approach. Starting from easily available and cheap chemicals through simple and time efficient procedures it affords 2-methylquinazolin-4-one. This work was part of our project focused on the design and synthesis biologically active styrylquinolines and quinazolines[13,14]. However we hope that the results presented here could be interesting also for broader audience.

Results and Discussion

Our approach is illustrated in scheme 1. Anthranilic acid was heated with acetic anhydride under microwave neat conditions provided 2-methyl-4*H*-3,1-beznoxazin-4-one (**II**). Then resulted product was reacted further with ammonia to provide 2-methylquinazolin-4(3H)-one(**III**).

In first step (scheme 1; a) by heating the neat mixture in boiling point of the acetic anhydride we were able to reduce all influential variables to time.



I **II** **III** **IIIa**

Scheme 1. Two step synthesis of 2-methylquinazolin-4(3H)-one a.) acetic anhydride, MW b.) ammonia, solid support, MW.

Increasing the time of heating gradually raise the yield as expected. Best condition for this step is 8-10 minutes as shown in figure 1. Further heating slightly lowered the amount of product and provided some oily substances that degrade the purity.

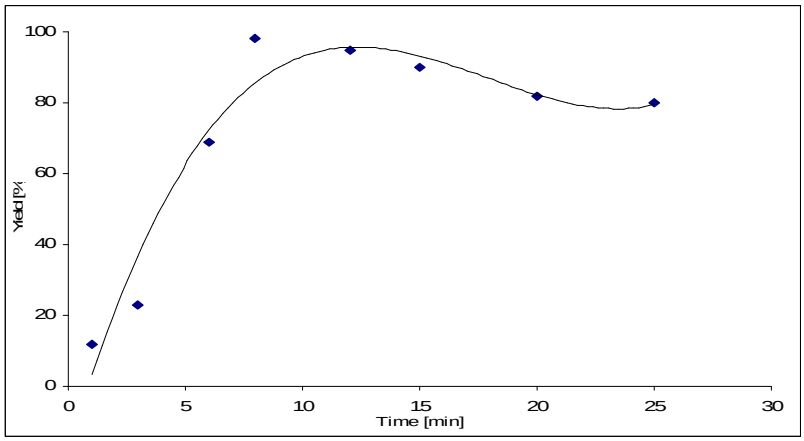


Figure 1. Optimization of synthesis of 2-methyl-4*H*-3,1-beznoxazin-4-one

The second step of the studied synthesis was optimized with MODDE-8 software. Influence of solid support was investigated as first variable. Each entry in table 1. is the mean of two experiments conducted for two different amounts of support. Best results were achieved with NaOH supported on alumina as shown in Table 1. Most solid supports provided considerable

amounts of undesired product (**IIIa**). Quite unexpected is that Al_2O_3 and NaOH alone give large amounts of **IIIa** and in case of pure hydroxide only traces of desired product (**III**) were detected.

Table 1. Synthesis of 2-methylquinazolin-4(3H)-ones on solid support. (+) – Product detected on TLC (-) – product not detected. All experiments were repeated twice with different amount of support (0.5 and 1 equiv).

Support	**II**	**III**	**IIIa**
None	+	trace	+
Al_2O_3	+	+	+
Montmorylonite K10	+	+	+
NaOH	+	trace	+
$NaHCO_3$	+	+	+
Na_2CO_3	+	+	+
NH_4Cl	+	+	+
$(NH_4)_2CO_3$	+	+	+
Al_2O_3*NaOH	–	+	trace
SiO_2*NaOH	+	+	+
NaCl	+	+	+
MgO	+	+	trace

Sodium hydroxide supported on alumina (Al_2O_3*NaOH) was selected for further optimization. In condition of this step three influential variables (time of heating, temperature and amount of support) can be distinguished. According to the software 19 experiments were designed. For especially interested entries additional experiments were done with intuitionally changed parameters. All results were taken into consideration during fitting the model (MLR-method). We have obtained good model R^2=0.94 and Q^2=0.70 with good validity (0.85) and very good reproducibility (0.92). The same can be derived from ANOVA plot and normal probability plot. In the Fig 2. we have shown the coefficient plot for the studied variables for the yield. Size of the

bar indicates the importance of the variable while the position (up or down) indicates the vector of influence (positive or negative). As one can see amount of support and time of heating are most important for optimization.

Interestingly we have found that however carrier is essential for this reaction its amount is inversely proportional to achieved yield.

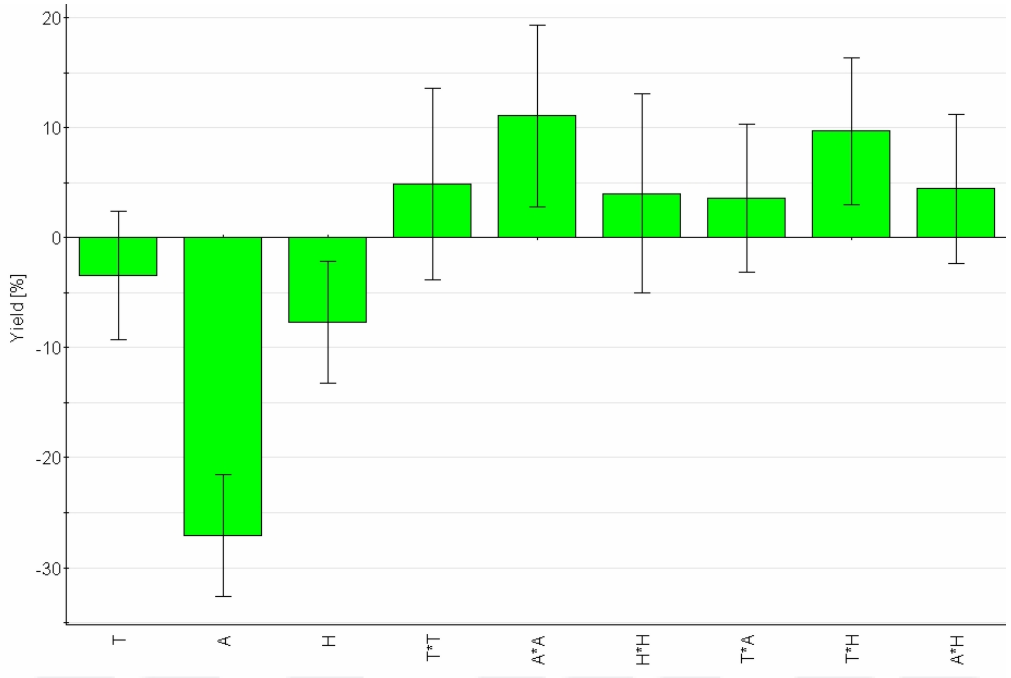
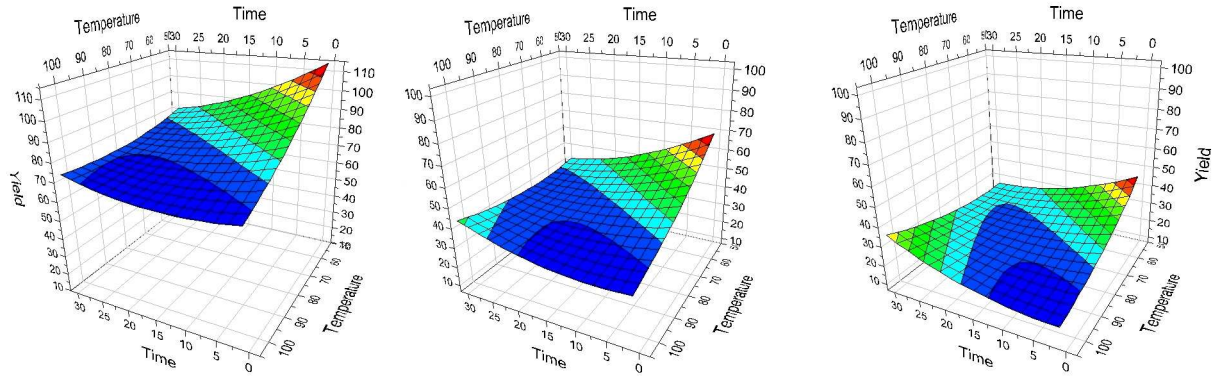


Figure 2. Influence of the analyzed variables: time (H), amount of support (A) and temperature (T) on the yield.

In Fig 3 yield predictions are shown for three different amounts of Al_2O_3*NaOH. It can be derived that small amount of carrier and short time of heating are preferably. The temperature should be in scope 60-70 ^oC. These findings are quite unexpected,



a.) **b.)** **c.)**

Figure 3. Predictions for the yield. a) 0.5 eqiv Al_2O_3*NaOH, b) 1 equiv, c) 1.5 equiv.

however could be clarified on the basis of known instability of 2-methyl-4*H*-3,1-beznoxazin-4-one which readily decompose in moisture or acidic conditions.

Materials and Methods

Chemicals and solvents were used for the syntheses as they were provided from common suppliers. TLC experiments were performed on alumina-backed silica gel 40, F_{254} plates (Merck, Darmstadt, Germany) using chloroform/acetone 1/1 as mobile phase. The plates were illuminated under UV (254 nm) and evaluated in iodine vapour. Melting points were determined on Boetius PHMK 05 (VEB Kombinat Nagema, Radebeul, Germany) and are uncorrected.

Microwave assisted synthesis were carried out on microwave reactor RM800 from Plazmatronika (Wroclaw, Poland) in monomode cavity. During all experiments temperature measurements were performed with external IR sensor. Power of microwave irradiation was continuously adjusted to keep the selected temperature (within 5^{o}C scope).

HPLC analyses were performed on Gynkotek with UVD34OU detector and Chromelon Software. RP-18 5µm column Lichrocart 250-4 part No. 240114 from Merck was applied.

Optimisation was performed with MODDE 8.0 software for design of experiments from Umetrics. 22 experiments (19 experiments for the design matrix and 3 additional experiments for check the best parameters) were done.

General procedure for preparation of solid support with NaOH.

To 20 g of oxid (Al_2O_3 or SiO_2) 70-230 mesh 18 mL of 20% solution of NaOH in water was added. Mixture was evaporated and grind with mortar to provide 25 g of support (7% NaOH, approximately 5% humidity).

General method for synthesis of 2-methyl-4*H*-3,1-beznoxazin-4-one.

Mixture of anthranilic acid (0.685 g, 5 mmol) and acetic anhydride (1.0 mL, 2 equiv) was irradiated for the selected period of time. After the heating was completed the reaction mixture was concentrated in high vacuum and the residue was subjected to HPLC analysis. For the best parameters the reaction was run with 50 mmol of the reagents and the crude product was extracted with dry n-heptane. Benzoxazinone is very susceptible to decomposition in the presence of water and was immediately reacted further. Purity of the product was above 95% as measured on HPLC.

General method for synthesis of 2-methylquinazolin-4(3H)-one.

2-methyl-4*H*-3,1-beznoxazin-4-one (0.4 g, 2.5 mmol), the selected solid support in 0.5, 1 and 1.5 weight equiv and NH_{3aq} (3.5 mL 50 mmol) as 25% water solution was mixed thoroughly and irradiated for the selected period of time. Then, the solvent was removed in vacuum and the residue was extracted with methanol. The methanolic solution contained 0.01g of crude product in 10 mL was subjected to HPLC analysis.

Conclusion

We have applied the design of experiment methodology for the optimization of solid state synthesis of quinazolinones. Two steps of the synthesis from easily available compounds were separately optimized. Several carriers for solid phase synthesis were explored and multivariable optimization was used. According to best parameters we obtained 2-methylquinazolin-4(3H)-one with 80% overall yield and purity over 95%.

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