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A microwave improvement in the synthesis of the quinazoline scaffold

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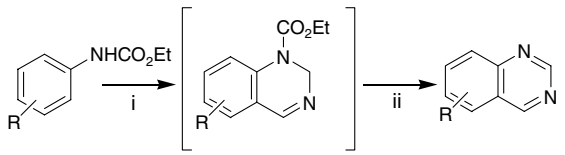
Abstract—A rapid and efficient microwave-assisted protocol is described that greatly improves a recent synthetic method developed for quinazoline synthesis. The synthetic protocol is based on the use of cycles of microwave irradiation. The optimization process is reported and the experimental results are compared with those of the conventional synthetic route.

The quinazoline nucleus is a very attractive and useful scaffold in medicinal chemistry: it can be found as a pharmacophore in a wide variety of biologically active compounds, such as antitumorals,[1] antibacterials,[2] antivirals,[3] and many other therapeutic agents.[4]

The interest in this heterocycle prompted us to set up a short and efficient route toward quinazoline nucleus, consisting of building the entire pyrimidine ring starting from simple anilines after N-protection as the ethyl carbamate. This method uses hexamethylenetetramine (HMTA) in TFA to perform starting aminomethylation and intramolecular cyclization to annulate the dihydropyrimidine ring, and then $K_3Fe(CN)_6$ in aqueous ethanolic KOH to obtain final oxidative dehydrogenation to the quinazoline (Scheme 1).[5]

The original method was carried out in two subsequent steps without isolating the reaction intermediate. In the first step, the *N*-carboxyethylanilines were refluxed in TFA with HMTA in a molar ratio 1:7 to achieve the double aminomethylation at both the *ortho*-position and the nitrogen atom of the protecting group yielding the dihydropyrimidine intermediate: by using a lower amount of HMTA the reaction did not reach completion. The reaction intermediate was not isolated but the reaction mixture needed to be diluted with HCl, filtered to eliminate the undissolved by-products and then evaporated. In the second step, the residue, dissolved in aqueous ethanolic KOH, was refluxed with $K_3Fe(CN)_6$ using a molar ratio 4:1 between oxidizing agent and starting product to give the final quinazoline.



Scheme 1. Conventional HMTA/TFA/$K_3Fe(CN)_6$ method. Reagents and conditions: (i) HMTA, TFA, reflux, 1 h. (ii) KOH aq EtOH, $K_3Fe(CN)_6$, reflux, 4 h.

The strength of this method, compared with those previously reported,[6] is the use of cheaper and easily available starting materials, the high selectivity and good yields, the reduction of synthetic steps and the applicability to a lot of aromatic amines,[7] while the weakness is the good but not excellent yields and the need of a dilution and alkalinization step before adding $K_3Fe(CN)_6$, so delaying the work up procedure. To improve on this new synthetic route, reducing the drawbacks, we decided to explore the application of MAOS (microwave-assisted organic synthesis) to our method. This non-classical heating technique significantly impacted synthetic and medicinal chemistry in the last few years, owing to its unique features of reducing reaction times while increasing yields and reducing work up procedures while minimizing reaction by-products.[8]

Since recently a new microwave-attempted improvement of an old quinazoline synthetic method was reported, even though once again three synthetic steps were

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required to perform quinazoline formation with global yields comparable to previously reported methods,[9] we tried to improve the quinazoline formation by applying microwave-assisted chemistry. The optimization of our HMTA/TFA/$K_3Fe(CN)_6$ method was achieved by using a single mode microwave reactor equipped with a cooling system for automatic microwave power regulation,[10] with the goal to reduce reagent amounts and work up procedures, in order to make the reaction more practically appealing and truly one-pot.

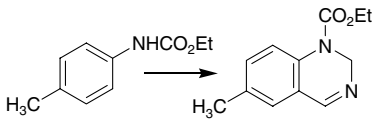
Two subsequent steps with different working conditions were involved in this synthetic process: the dihydropyrimidine formation, requiring an acid medium, and the final aromatization, requiring a basic one. In this way, the reaction had to be carried out by two microwave irradiation steps with an intermediate stop to change the reaction medium and to introduce the oxidizing agent. The two irradiation steps were separately optimized by using *N*-carbethoxy-4-methylaniline as reference compound to set up the reaction conditions (Table 1).

An irradiation at 110 °C for 10 min was found the best time and temperature conditions for complete dihydropyrimidine formation: these conditions allowed to reduce the HMTA/aniline ratio from 7:1, as used with classical heating, to 1:1 with microwave irradiation and to halve the TFA volume required. As a consequence, there was no need to work up the reaction mixture to eliminate the HMTA excess and the reaction mixture was directly diluted and made alkaline with aqueous ethanolic KOH and treated with $K_3Fe(CN)_6$.

The second irradiation step was studied to optimize time and temperature conditions. First of all, the amount of KOH required was strongly reduced owing to the reduction of the volume of acid in the previous step. Moreover, the procedures of irradiation and addition of the oxidizing agent were of critical importance to maximize reaction yield. The synthetic protocol was based on the use of several cycles of microwave irradiation rather than a single irradiation step.[11]

With a single addition and irradiation step, the reaction never reached completion, even with high temperatures,

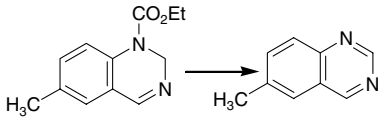
Table 1. Optimization of dihydropyrimidine formation



Entry	Time (min)	Temperature (°C)	Yield[a] (%)
1	10	100	95
2	10	110	98
3	10	120	93
4	5	110	90

Reagents and conditions: aniline (1 mmol) and HMTA (1 mmol) in TFA (3 mL) were irradiated in a monomode microwave reactor.
[a] Yield of isolated product.

Table 2. Optimization of quinazoline formation



Entry	Time (min)	Temperature (°C)	Number of cycles	Yield[a] (%)
1	10	100	1	60
2	20	100	1	68
3	30	100	1	68
4	10	100	2	75
5	10	100	3	90
6	10	100	4	97

Reagents and conditions: dihydropyrimidine (1 mmol) and $K_3Fe(CN)_6$ (totally 4 mmol) in aq ethanolic (water/EtOH: 1:1) 10% KOH (50 mL) were irradiated in a monomode microwave reactor.
[a] Yield of isolated product.

prolonged reaction times, and/or increasing oxidizing reagent amounts. Therefore, the reaction was carried out with more than one irradiation cycle for shorter times adding a stoichiometric amount of $K_3Fe(CN)_6$ for each cycle. The best result was achieved at 100 °C with four irradiation cycles of 10 min each (Table 2).

Once standard reaction time and temperature conditions were set up,[12] the protocol was applied to other N-protected anilines, on which quinazoline synthesis was already performed by the conventional HMTA/TFA/$K_3Fe(CN)_6$ method.[5] The results are summarized in Table 3, comparing the yield obtained by conventional heating to those obtained by microwave irradiation. In every instance, the use of microwave irradiation was greatly superior to conventional heating with yields ranging from 80% up to 95%, that means more than doubled if compared with classical heating. The number of irradiation cycles in the second step varied from 3 to 4 according to the intermediate dihydropyrimidine.

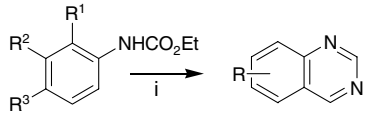
It should be noted that a methoxy or amino substitution on position 3 of starting aniline (Table 3, entries 5, 6, 8, and 9) activates selectively the position *para* to the substituent without formation of other possible isomers, so proving the regioselectivity of pyrimidine annulation, as already reported.[5]

In the synthesis of 6-chloroquinazoline, the resulting yield was very poor (19%) even with the microwave improvement. However, the yield was increased up to 55% carrying out the first step in three irradiation cycles of 25 min each using a threefold excess of HMTA for each cycle and then performing the second irradiation step in the usual way.

Besides the improvement of the yield and the reduction of reaction time, the microwave-assisted method reduced solvent and reagent amounts and made the reaction cleaner and thus easier to work up.

In conclusion, we have developed a rapid, high-yielding, and user-friendly protocol for the one-pot synthesis of

Table 3. Comparison between conventional synthesis and MAOS



Entry	Starting product			Product	Yield		Number of cycles
	R^1	R^2	R^3		(a)	(b)	
1	H	H	CH_3	6-Methylquinazoline	49	**95**	4
2	H	H	OCH_3	6-Methoxyquinazoline	19	**92**	3
3	H	H	OH	6-Hydroxyquinazoline	24	**86**	3
4	H	H	$NHCO_2Et$	6-Aminoquinazoline	54	**90**	3
5	H	OCH_3	H	7-Methoxyquinazoline	22	**79**	3
6	H	$NHCO_2Et$	H	7-Aminoquinazoline	45	**91**	3
7	CH_3	$NHCO_2Et$	H	7-Amino-8-methylquinazoline	38	**83**	4
8	H	$NHCO_2Et$	CH_3	7-Amino-6-methylquinazoline	44	**80**	3
9	H	$NHCO_2Et$	OCH_3	7-Amino-6-methoxyquinazoline	43	**84**	3
10	H	H	Cl	6-Chloroquinazoline	15	**55**[a]	4

Reagents and conditions: (i) (1). HMTA, TFA, MW, 110 °C, 10 min. (2). KOH aq EtOH, $K_3Fe(CN)_6$, 100 °C, three or four cycles of 10 min each. (a) Yield of conventional synthesis. (b) Yield of microwave-assisted reaction.
[a] See text for details.

quinazoline from simple and easy available starting materials.

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10. The monomode reactor (CEM Discover®) is equipped with PowerMax® technology that allows simultaneous cooling of a reaction with compressed gas, while irradiating it with microwave energy (enhanced microwave synthesis). Thus, energy can be continuously applied while keeping bulk temperature at a set level: this feature prevents unwanted side reactions and allows for cleaner and faster reactions. For details: http://www.cemsynthesis.com.
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12. *General MW experimental procedure* (performed in a CEM Discover® monomode reactor with the temperature monitored by a built-in infrared sensor). A mixture of carbamate (1 mmol) and HMTA (1 mmol) in TFA (3 mL) was microwave irradiated at 110 °C (power set point 80 W; ramp time 1 min; hold time 10 min). After cooling, the mixture was diluted with aqueous ethanolic (water/EtOH: 1:1) 10% KOH (50 mL) and the solution was microwave irradiated at 100 °C for several cycles (power set point 110 W; ramp time 4 min; hold time 10 min for each cycle) (see Table 3 for the number of cycles), adding $K_3Fe(CN)_6$ (1 mmol) for each irradiation cycle. After cooling, the mixture was diluted with water (50 mL), extracted with EtOAc or toluene (5×20 mL), and the organic phase was evaporated under reduced pressure to give the final quinazoline. Yields are reported in the text (Table 3). The analytical data were in agreement with the literature values.[5]