# MICROWAVE ENHANCED SYNTHESIS OF QUINAZOLINES IN SOLVENT-FREE CONDITION

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**Abstract**
Reaction of anthrarnilic acid derivatives with formamide in solvent-free condition on silica gel, acidic alumina, and montmorillonite K-10 under microwave irradiation gave quinazolines in good yields.

## Introduction

Quinazolines are a wide family of compounds with well-known pharmaceutical properties.(1-6) They have a wide range of activities e.g. analgesic, narcotic, anti-malaria, sedative or hypoglycemic activity. There are many methods for the synthesis of quinazolines (6) such as:

a) Nimentowski reaction, condensation of anthranilic acid with amides (7). b) Cyclization of o-amidobenzamides (8). c) Condensation of o-aminobenzonitriles and anhydrides (9). d) Reaction of anthranilic acid derivatives with esters and imidates (10). e) Grimvel, Guether and Moghan synthesis (6). These procedures employ high temperatures, various solvents and need long reaction times.

Combination of supported reagents and microwave irradiation were used to carry out a wide range of reactions in solvent-free condition (11). Following our research works about solid phase synthesis using microwave irradiation (12), herein, we wish to report reaction of anthranilic acid derivatives with formamide in neat condition and on silica gel, acidic alumina and montmorillonite K-10 under microwave irradiation as a useful method for the synthesis of quinazoline derivatives.

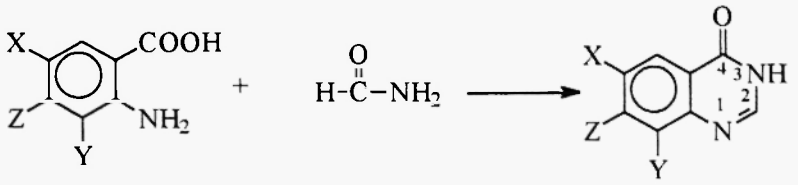

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**Table 1:** Synthesis of Quinazolines in solvent-free condition on silica gel, acidic alumina, montmorillonite K-10, under microwave irradiation.

| | | | | Yield (%)* | | | |
|---|---|---|---|---|---|---|---|
| **Entry** | X | Y | Z | Neat condition | Acidic alumina | Silica gel | Montmorillonite K-10 |
| **a** | H | H | H | 60 | 75 | 85 | 88 |
| **b** | Br | H | H | 54 | 70 | 80 | 82 |
| **c** | Br | Br | H | 34 | 46 | 35 | 51 |
| **d** | H | H | Cl | 56 | 77 | 91 | 94 |

*In all experiments time of irradiation was 4 minutes.

**Reported reaction times for the synthesis of these compounds were 3 hours.

## Results and discussion

All compounds are known and identified with their reported IR, $^1$H-NMR spectroscopic data and melting points. In $^1$H-NMR spectra of compound **3a**, H-2 shows a singlet at δ 8.10 ppm and N-H shows a broad singlet at 12.20. Presence a sharp carbonyl stretching bond at 1690 cm$^{-1}$ shows the major oxo-form for quinazolines. The results seen in Table 1 clearly show that running the reaction in presence of solid support give better yields than neat condition. The best yield obtained with montmorillonite K-10 as a solid support.

## Conclusions

We developed a general and efficient method for the synthesis of quinazolines; simple set-up and work-up, good yields and short reaction times, elimination of solvent and reflux condition are advantages of this method.

## Experimental:

Melting points are uncorrected and measured on an electrothermal 9100 melting point apparatus. IR spectra were run on a Shimadzu IR-408 spectrometer and expressed in cm$^{-1}$ (KBr), $^1$H-NMR spectra were recorded on FT-NMR Bruker AC-80 (80MHz) in $CDCl_3$ solution using TMS as internal standard. A domestic microwave oven (Moulinex 2735A) at 2450MHz (100% Power 850W) was used in all experiments.

*General procedure for the synthesis of quinazolines:*

Anthranilic acid derivatives (2 mmole), 360 mg formamide (8mmole), and silica gel, acidic alumina and montmorillonite K-10 as acidic solid supports were mixed in a mortar, then transferred into a beaker and irradiated for 4 min. The progress of reaction were monitored by TLC. Dichloromethane was added to the mixture, filtered and washed with water. Organic phase was separated and after drying with sodium sulfate and evaporation with rotary evaporator a solid was appeared.

Further purification by column chromatography with petroleum ether and dichloromethane (30:70) or crystallization with ethanol gave the desired products.

**3,4-dihydro-4-oxo-quinazoline (3a):**
m.p.= 211-213°C [Lit (6,13): 209, 215.5-216.5°C]
IR (KBr) $cm^{-1}$, 1690, 1585; $^1$H-NMR (DMSO) δ (ppm), 7.30-8.00 (m 4H, aromatic), 8.10 (s, 1H, H-2), 12.20 (brs, 1H, NH).

**6-bromo-3,4-dihydro-4-oxo-quinazoline (3b):**
m.p.= 254°C [Lit (6, 14): 258, 272°C)
IR (KBr, $cm^{-1}$) 1700, 1610; $^1$H-NMR (DMSO) (δppm): 6.90-7.50 (m, 3H, aromatic), 7.70 (s, 1H, H-2), 11.7 (brs, 1H, NH).

**6,8-dibromo-3,4-dihydro-4-oxo-quinazoline (3c):**
m.p.= 275-277°C [Lit (6, 9): 279°C)
IR (KBr, $cm^{-1}$) 1680, 1610; $^1$H-NMR (DMSO) (δppm): 7.50-8.40 (m, 2H, aromatic), 8.50 (s, 1H, H-2), 12.50 (brs, 1H, NH).

**7-chloro-3,4-dihydro-4-oxo-quinazoline (3d):**
m.p.= 254-255°C [Lit (6, 15): 254-255.5°C)
IR (KBr, $cm^{-1}$) 1680, 1610; $^1$H-NMR (DMSO) (δppm): 7.40-8.20 (m, 3H, aromatic), 8.00 (s, 1H, H-2), 12.40 (brs, 1H, NH).

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