

Comparative study between the Titanium Phosphate TiP_2O_7 and the Phosphate Fertilizers in the catalysis of the Quinazolin-4(3H)-one derivatives synthesis

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Abstract: A simple and efficient method for the synthesis of quinazolin-4(3H)-one derivatives via condensation of anthranilamide with aromatic aldehyde catalyzed by monoammonium phosphate (MAP), diammonium phosphate (DAP), and triple superphosphate (TSP), were developed. The modification of these three phosphate fertilizers using titanium tetrachloride ($TiCl_4$) has increased their catalytic efficiency. The prepared titanium phosphate (TiP_2O_7) was characterized using microscopic and spectroscopic methods, namely X-ray diffraction (XRD), scanning electron microscopy (SEM), energy dispersive X-ray analysis (EDX), and infrared spectroscopy (IR). The TiP_2O_7 was applied for the first time as a heterogeneous catalyst in quinazolin-4(3H)-ones synthesis. High yields and short reaction times were observed in the determined optimal condition (solvent nature, volume, and catalyst amount). This study shows that the TiP_2O_7 presents an exciting catalytic activity and long-term durability compared to those of MAP, DAP, and TSP.

Keywords: heterogeneous catalyst; quinazolin-4(3H)-ones; TiP_2O_7 ; recyclability.

1. Introduction

The quinazolin-4(3H)-one derivatives present an important class of heterocyclic compounds, which attracted considerable attention in these last years, due to their pharmacological and biological activities such as antitumor drugs ¹, antibacterial ², anti-hypertensive ³, anti-inflammatory ⁴, anti-HIV ⁵, antifungal ⁶, nonpeptide CCK-B antagonists ⁷, antiallergic ⁸, insecticidal ⁹, and inhibition of humane erythrocyte purine nucleoside phosphorylase ¹⁰. In addition, the quinazolin-4(3H)-ones are the basic building blocks in the synthesis of natural products ¹¹ and the constituents of some isolated natural alkaloids ¹².

Due to the importance of quinazolin-4(3H)-one derivatives, several processes for their Synthesis were developed in the presence or absence of the catalyst. Indeed, the quinazolin-4(3H)-one derivatives were previously synthesized by the thermolysis of 3-arylideneamine-1,2,3-benzotriazine-4-ones in paraffin oil at 300°C ¹³ or condensation of anthranilamide with aldehydes, ketones or isatoic anhydride with ammonium acetate using various catalysts such as ionic liquid [BDBIm]Br ¹⁴,

Sc(OTf)₃ ¹⁵, $TiCl_4$ -Zn ¹⁶, $FeCl_3 \cdot 6H_2O$ ¹⁷, $Ni(NO_3)_2 \cdot 3H_2O$ ¹⁸, $CuCl_2$ in ethanol ¹⁹, p-toluenesulfonic acid/DDQ ²⁰ and $SbCl_3$ under microwave irradiation ²¹. Recently different catalysts were reported, such as sulfated MOF-808 ²², H_3PO_3 ²³, $FeCl_3 \cdot 6H_2O \cdot H_2O/PEG-400$ ²⁴, Cu@PEI-MGO ²⁵ and $Pd(PPh_3)_4$ ²⁶.

Most of these methods present some disadvantages, such as low yields, hard reaction conditions, prolonged reaction time, and the use of expensive, non-recyclable, or homogeneous catalysts. Therefore, the development of a simple, economical, and efficient preparation method is highly desirable. For this, the application of heterogeneous catalysts, which are known by their comfortable handling, simple workup, and recyclability, is considered the best method for the quinazolin-4(3H)-ones synthesis.

As a continuation of the previous works developed by our researchers ²⁷⁻³⁹, which consist on the valorization of Moroccan phosphates in the field of organic synthesis, and the development of green and sustainable chemistry, this paper reports the first and an easy preparation method for TiP_2O_7 from the modifications of phosphate fertilizers MAP, DAP and

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Email address: youmerroun@yahoo.com, souizi@yahoo.com
DOI: <http://dx.doi.org/10.13171/mjc106020201368ym>

Received February 29, 2020
Accepted April 26, 2020
Published June 20, 2020

TSP by titanium tetrachloride (TiCl_4). The characterization of TiP_2O_7 was realized using spectroscopic and microscopic techniques such as XRD, IR, SEM, and EDX.

Due to the chemical stability, non-hazardous nature, relatively low cost, and easy availability of this support ⁴⁶, it has been used previously by other researchers as electrode material ⁴⁰, solid electrolyte ⁴¹, fuel cell ⁴², a negative electrode for aqueous lithium-ion batteries ⁴³, and photocatalyst ^{44,45}.

The novelty of the present study is the application of TiP_2O_7 for the first time as a heterogeneous catalyst in the quinazolin-4(3H)-ones derivatives synthesis.

The catalytic activity of the prepared support (TiP_2O_7) has been compared with that of MAP, DAP, and TSP used in the quinazolin-4(3H)-one derivatives synthesis.

2. Experimental

2.1. Materials and Instrumentation

The reagents and solvents were purchased from SIGMA ALDRICH. For all reactions, the purity of the quinazolin-4(3H)-one derivatives were monitored by thin-layer chromatography (TLC) using aluminum layers coated with F254 silica gel (Merck) plates. The

melting points were recorded on a hot Kofler. ^1H NMR and ^{13}C NMR spectra were recorded in Bruker spectrometer in the presence of DMSO-d_6 at 300 and 75 MHz, respectively. The X-ray diffraction spectra were obtained by using a PANalytical X'Pert3 Powder diffractometer operated at 45 kV and 40 mA with $\text{CuK}\alpha$ radiation ($\lambda = 1.54178 \text{ \AA}$). Infrared Spectrum was made on a VERTEX 70 spectrometer using KBr pellets. The Scanning Electronic Microscopy (SEM) and EDX analysis were carried out on VEGA3 TESCAN microscope equipped with an energy dispersive X-ray spectrometer with an accelerating potential of 15 kV, and a beam current of 20 mA. The catalyst diameters were determined from the SEM micrographs at random locations by using Image J software.

2.2. Preparation of TiP_2O_7

The modification of the phosphates fertilizer MAP, DAP, or TSP was realized by adding titanium tetrachloride (TiCl_4) (ratio of TiCl_4 / phosphate fertilizer of 1/2). The mixture was agitated for one hour, then evaporated under vacuum. The solid obtained was dried at 150°C for one night, ground and calcined at 500°C for two hours to get TiP_2O_7 which is then crushed, sieved, and stored in a flacon. Figure 1 shows the TiP_2O_7 preparation method.

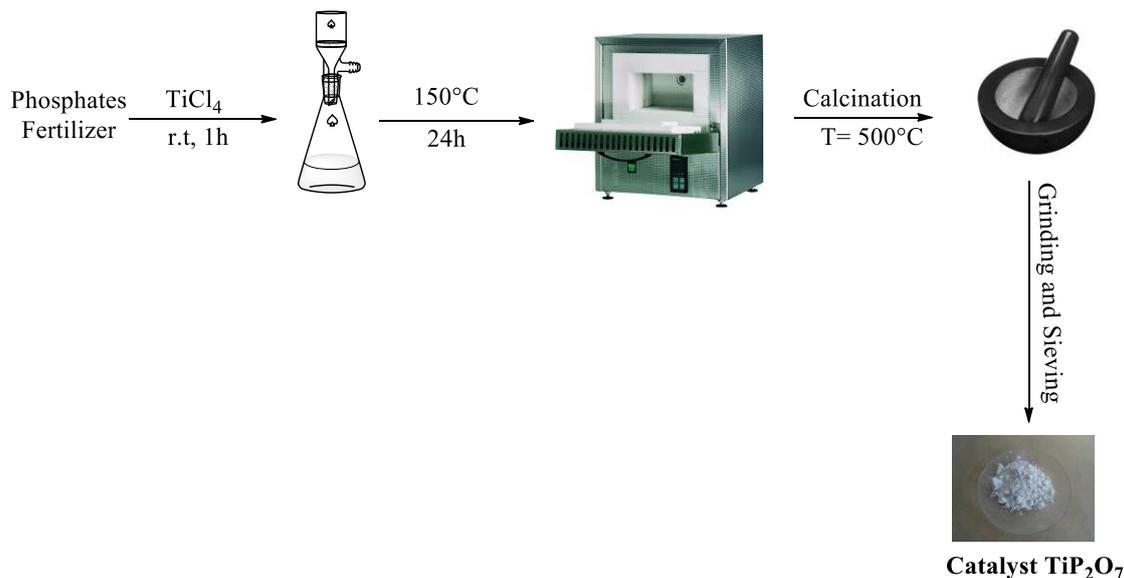


Figure 1. Different steps of titanium phosphate preparation

2.3. General Procedure for quinazolin-4(3H)-one derivatives synthesis

In a round bottom flask of 50 mL, 1 mmol of aromatic aldehyde and 1 mmol of anthranilamide was dissolved in DMF (1 mL) in the presence of MAP, DAP, TSP or TiP_2O_7 as a catalyst and heated at reflux. The reaction was monitored by thin-layer chromatography (TLC) (chloroform/methanol, 8/2). After completion of the reaction, the mixture was cooled at room temperature. Then, dichloromethane (5 mL) was added to the mixture to separate the catalyst by simple filtration; the filtrate was evaporated until the

precipitates were formed. The product was purified by recrystallization with ethanol to obtain the quinazolin-4(3H)-one derivatives. The catalyst may be reactivated later by washing with ethanol to remove the products that may be present on its surface and then dried before being reused.

The products obtained were characterized on the basis of comparison of their melting points and their ^1H and ^{13}C NMR spectroscopic data with those reported in the literature, which show a good agreement ⁴⁷⁻⁵⁰.

2.4. Characterization Data of All Compounds

2-(4-chlorophenyl)quinazolin-4(3H)-one (3a)

¹H NMR (300 MHz, DMSO-d₆) δ(ppm): 12.63 (s, 1H, NH), 8.14-8.21 (m, 3H, H-Ar), 7.85 (t, J=7.6 Hz, 1H, H-Ar), 7.74 (d, J=7.8 Hz, 1H, H-Ar), 7.62 (d, J=8.7 Hz, 2H, H-Ar), 7.54 (t, J=7.2 Hz, 1H, H-Ar).

¹³C NMR (75 MHz, DMSO-d₆) δ(ppm): 162.68, 151.82, 148.99, 136.76, 135.14, 132.02, 130.09, 129.16, 127.96, 127.25, 126.34, 121.45.

2-(4-nitrophenyl)quinazolin-4(3H)-one (3b)

¹H NMR (300 MHz, DMSO-d₆) δ(ppm): 12.84 (s, 1H, NH), 8.35-8.43 (m, 4H, H-Ar), 8.18 (d, J=7.8 Hz, 1H, H-Ar), 7.88 (t, J=8.1 Hz, 1H, H-Ar), 7.80 (d, J=7.9 Hz, 1H, H-Ar), 7.58 (t, J=7.51 Hz, 1H, H-Ar).

¹³C NMR (75 MHz, DMSO-d₆) δ(ppm): 162.57, 151.45, 149.43, 148.77, 139.01, 135.28, 129.78, 128.21, 127.84, 126.40, 124.13, 121.70.

2-(4-dimethylaminophenyl)quinazolin-4(3H)-one (3c)

¹H NMR (300 MHz, DMSO-d₆) δ(ppm): 12.01 (s, 1H, NH), 8.08-8.14 (m, 3H, H-Ar), 7.77 (t, J=7.8 Hz, 1H, H-Ar), 7.65 (d, J=8.1 Hz, 1H, H-Ar), 7.41 (t, J=7.5 Hz, 1H, H-Ar), 6.80 (d, 2H, J=8.7 Hz, H-Ar), 3.01 (s, 6H, N(CH₃)₂).

¹³C NMR (75 MHz, DMSO-d₆) δ(ppm): 162.78, 152.86, 152.78, 149.90, 134.73, 129.35, 127.47, 126.25, 125.75, 120.96, 119.52, 111.76, 40.11.

2-(4-methylphenyl)quinazolin-4(3H)-one (3d)

¹H NMR (300 MHz, DMSO-d₆) δ(ppm): 12.50 (s, 1H, NH), 8.09-8.17 (m, 3H, H-Ar), 7.83 (t, J=7.6 Hz, 1H, H-Ar), 7.72 (d, J=8.1 Hz, 1H, H-Ar), 7.51 (t, J=7.2 Hz, 1H, H-Ar), 7.36 (d, J=7.8 Hz, 2H, H-Ar), 2.38 (s, 3H, CH₃).

¹³C NMR (75 MHz, DMSO-d₆) δ(ppm): 162.76, 152.70, 149.27, 141.94, 135.05, 130.05, 129.67, 127.86, 127.28, 126.87, 126.32, 121.34, 21.47.

2-phenylquinazolin-4(3H)-one (3e)

¹H NMR (300 MHz, DMSO-d₆) δ(ppm): 12.51 (s, 1H, NH), 8.15-8.21 (m, 3H, Ar-H), 7.84 (t, J=7.5 Hz, 1H, Ar-H), 7.75 (d, J=8.1 Hz, 1H, Ar-H), 7.52-7.63 (m, 4H, Ar-H).

¹³C NMR (75 MHz, DMSO-d₆) δ(ppm): 162.80, 152.84, 149.14, 135.09, 133.19, 131.88, 129.09, 128.24, 127.90, 127.07, 126.63, 121.42.

2-(2-hydroxyphenyl)quinazolin-4(3H)-one (3f)

¹H NMR (300 MHz, DMSO-d₆) δ(ppm): 12.62 (s, 1H, NH), 9.90 (s, 1H, OH), 8.23 (d, J=7.9 Hz, 1H, H-Ar), 8.16 (d, J=7.8 Hz, 1H, H-Ar), 7.87 (t, J=7.6 Hz, 1H, H-Ar), 7.77 (d, 1H, H-Ar), 7.56 (t, J=7.4 Hz, 1H, H-Ar), 7.47 (t, J=7 Hz, 1H, H-Ar), 7.01 (m, 2H, H-Ar).

¹³C NMR (75 MHz, DMSO-d₆) δ(ppm): 161.45, 160.01, 153.84, 146.11, 135.20, 133.74, 127.76, 126.93, 126.07, 120.72, 118.88, 117.91, 113.83.

2-(4-hydroxy-3-methoxyphenyl)quinazolin-4(3H)-one (3g)

¹H NMR (300 MHz, DMSO-d₆) δ(ppm): 12.35 (s, 1H, NH), 9.76 (s, 1H, OH), 8.12 (d, J=8.1 Hz, 1H, Ar-H), 7.68-7.83 (m, 4H, Ar-H), 7.46 (t, J=7.8 Hz, 1H, Ar-H), 6.92 (s, 1H, Ar-H), 3.90 (s, 3H, OCH₃).

¹³C NMR (75 MHz, DMSO-d₆) δ(ppm): 162.84, 152.49, 150.42, 149.48, 147.95, 134.98, 127.69,

126.40, 126.28, 123.86, 121.96, 121.05, 115.89, 111.80, 56.25.

2-(4-methoxyphenyl)quinazolin-4(3H)-one (3h)

¹H NMR (300 MHz, DMSO-d₆) δ(ppm): 12.42 (s, 1H, NH), 8.12-8.20 (m, 3H, Ar-H), 7.82 (t, J=7.5 Hz, 1H, Ar-H), 7.72 (d, J=7.8 Hz, 1H, Ar-H), 7.47 (t, J=7.2 Hz, 1H, Ar-H), 7.11 (d, J=7.8 Hz, 2H, Ar-H), 3.83 (s, 3H, OCH₃).

¹³C NMR (75 MHz, DMSO-d₆) δ(ppm): 162.37, 161.93, 152.40, 148.95, 135.01, 129.32, 127.11, 126.72, 126.43, 125.3, 121.32, 113.85, 55.52.

2-(4-bromophenyl)quinazolin-4(3H)-one (3i)

¹H NMR (300 MHz, DMSO-d₆) δ(ppm): 12.59 (s, 1H, NH), 8.10-8.17 (m, 3H, Ar-H), 7.81 (t, J=7.6 Hz, 1H, Ar-H), 7.70 (d, J=8.1 Hz, 1H, Ar-H), 7.60 (d, J=8.1 Hz, 2H, Ar-H), 7.51 (t, J=7.8 Hz, 1H, Ar-H).

¹³C NMR (75 MHz, DMSO-d₆) δ(ppm): 162.54, 151.89, 149.10, 135.27, 132.53, 132.15, 130.28, 128.01, 127.35, 126.50, 125.71, 121.49.

2-(4-hydroxyphenyl)quinazolin-4(3H)-one (3j)

¹H NMR (300 MHz, DMSO-d₆) δ(ppm): 12.32 (s, 1H, NH); 10.09 (s, 1H, OH), 8.08-8.12 (m, 3H, H-Ar), 7.75-7.84 (m, 1H, H-Ar), 7.68 (d, J=8 Hz, 1H, H-Ar), 7.45 (t, J=7.5 Hz, 1H, H-Ar), 6.86 (d, J=7.8 Hz, 2H, H-Ar).

¹³C NMR (75 MHz, DMSO-d₆) δ(ppm): 163.25, 161.01, 149.10, 134.56, 129.47, 127.12, 125.95, 125.91, 123.17, 115.32.

2-(3,4-dimethoxyphenyl)quinazolin-4(3H)-one (3k)

¹H NMR (300 MHz, DMSO-d₆) δ(ppm): 12.43 (s, 1H, NH), 8.12 (d, J=8.1 Hz, 1H, H-Ar), 7.80-7.84 (m, 2H, H-Ar), 7.68 (d, J=8 Hz, 1H, H-Ar), 7.51 (d, J=8.1 Hz, 1H, H-Ar), 7.43 (d, J=7.8 Hz, 1H, H-Ar), 7.14-7.10 (d, J=8 Hz, 1H, H-Ar), 3.85 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃).

¹³C NMR (75 MHz, DMSO-d₆) δ(ppm): 163.13, 152.27, 151.32, 149.76, 149.48, 134.93, 127.90, 126.52, 126.38, 125.31, 120.30, 111.09, 110.24, 62.15, 57.32.

3. Result and Discussion

3.1. Characterization of TiP₂O₇

The powder X-ray diffraction (XRD) shows the absence of secondary peaks, which confirms the formation of a single phase of TiP₂O₇ (Figure 2). The diffraction peaks at 19.47°, 22.39°, 25.16°, 27.89°, 32.20°, 38.57°, 42.20°, 48.80°, 52.12°, 58.23° and 62.38° belonged respectively to the crystalline plane (511), (600), (630), (721), (660), (933), (960), (12 3 0), (12 6 0), (14 4 2) and (11 11 1). All the positions of the prepared support's XRD peaks shown a good agreement with those reported in the literature ^{43,51-54}. All reflections can be indexed in the cubic system using the Pa-3 (205) space group, with crystalline parameters a = b = c = 23.6341 Å (JCPDS No. 38-1468). The Debye-Scherrer equation determined the average particle crystallite size (D):

$$D = \frac{0.9\lambda}{\beta \cos\theta}$$

Where, λ is the X-ray incident wavelength ($\text{CuK}\alpha = 0.154178 \text{ nm}$), β -full width at half maximum (FWHM) of the diffraction line and θ is the diffraction angle. The average crystalline size of TiP_2O_7 was found to be equal to 32.15 nm.

Assuming that the particles are spherical, the specific surface area was calculated by using the Sauter formula:

$$S = \frac{6 \times 10^3}{\rho \times D}$$

Where S is the specific surface area in $\text{m}^2 \cdot \text{g}^{-1}$, ρ is the density of synthesized material (TiP_2O_7) in $\text{g} \cdot \text{cm}^{-3}$, and D is the particle diameter in nm. The density of TiP_2O_7 is 3.052 g/cm^3 ⁵⁵, and the average crystallite size is 32.15 nm. Thus, the calculated value of S was found to be $61.14 \text{ m}^2/\text{g}$.

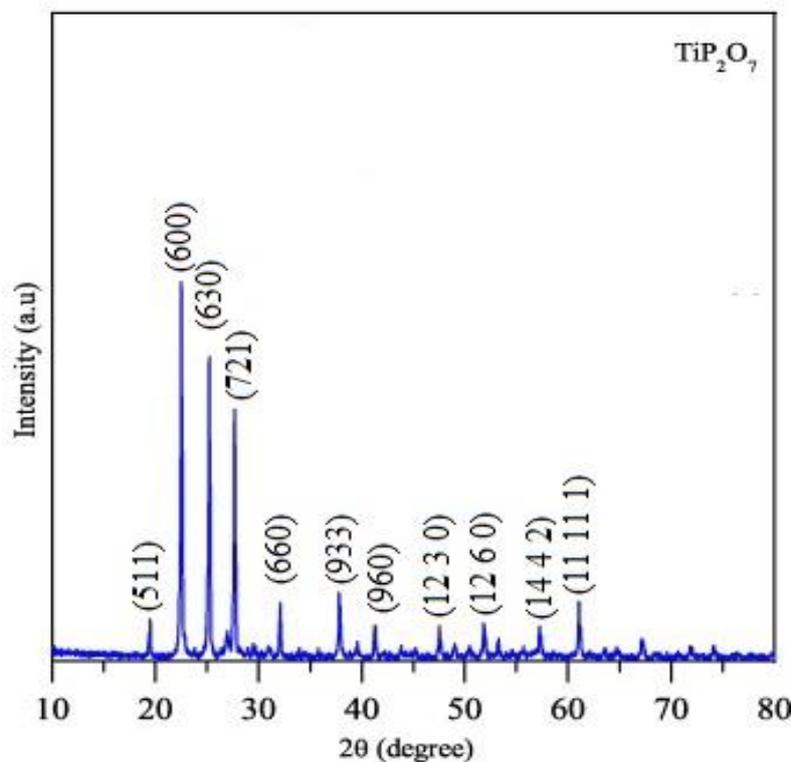


Figure 2. XRD analysis of TiP_2O_7

The morphology of TiP_2O_7 was studied by scanning electron microscopy (SEM) (Figure 3). The SEM images show that the TiP_2O_7 consists of a set irregular

spherical particle shape with an average diameter of 32 nm. The obtained value indicates a good agreement with that calculated from XRD.

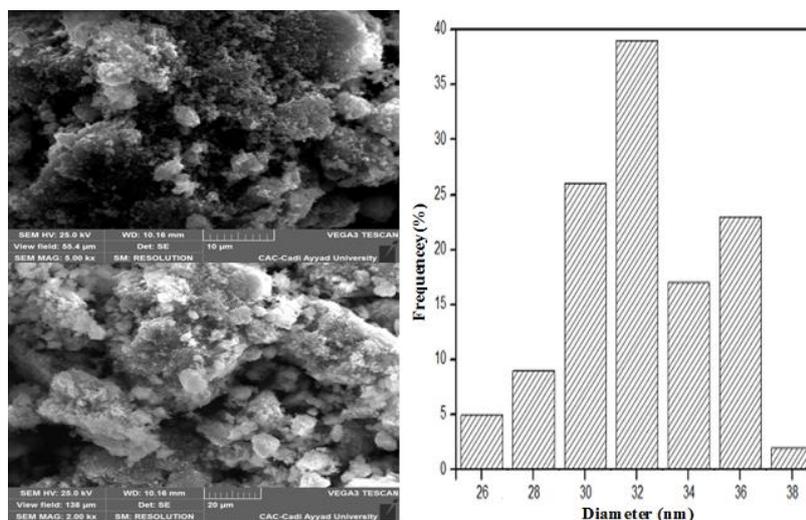


Figure 3. SEM and size histograms images of TiP_2O_7

To determine the elements present in the prepared sample, the analysis of its surface was carried out by

the spectrum of energy dispersion (EDX) (Figure 4).

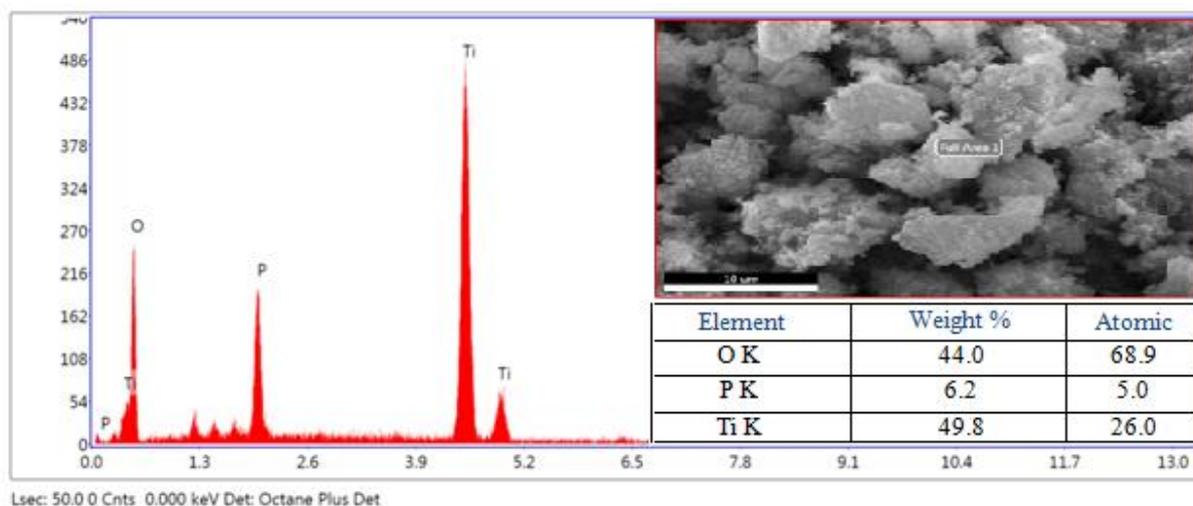


Figure 4. EDX analysis of the chemical elements constituent TiP_2O_7

The energy dispersive X-ray analysis (EDX) of TiP_2O_7 shows the presence of the elements constituent TiP_2O_7 , such as phosphorus, oxygen, and titanium. The comparison of the percentage of the element obtained by EDX analysis with this reported in the literature shows a good agreement⁵⁶.

The TiP_2O_7 characterization was completed by the infrared spectroscopy analysis (Figure 5). The peaks located towards 3477.80, 3414.99, and 1632.33 cm^{-1}

are attributed to the vibration characteristics of O-H group due to the presence of the water molecule adsorbed on the surface of TiP_2O_7 . The maximum of the broad peak between 1000 and 1200 cm^{-1} assigned to P-O vibrations. A band at 622.5 cm^{-1} corresponds to the vibration O-P-O. While, two characteristics bands of the bridging P-O-P are assigned at 954.68 and 732.92 cm^{-1} , and the bands located at 567.31 and 504.49 cm^{-1} are associated with the vibration of O-Ti-O⁵⁶⁻⁶⁰.

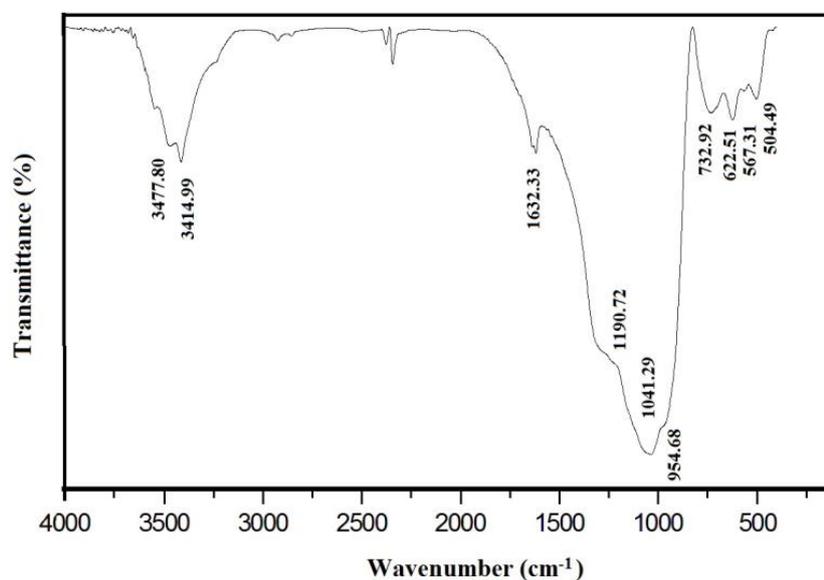
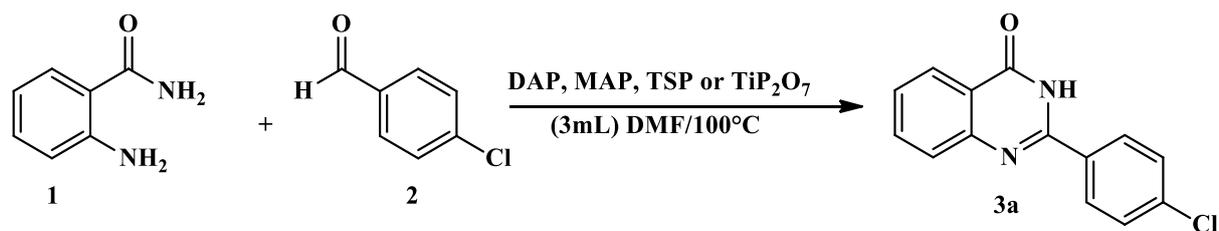


Figure 5. Infrared spectrum of TiP_2O_7

3.2. Evaluation of MAP, DAP, TSP, and TiP_2O_7 catalytic activity in the quinazolin-4(3H)-ones synthesis

The determination of TiP_2O_7 , MAP, DAP, and TSP catalytic efficiency was the principal objective of this

work. For this, they were applied as a heterogeneous catalyst in the quinazolin-4(3H)-one synthesis. The condensation of anthranilamide and 4-chloro benzaldehyde was chosen as a model reaction (Scheme 1) (Table 1).



Scheme 1. Synthesis of quinazolin-4(3H)-one catalyzed by MAP, DAP, TSP or TiP₂O₇

Table 1. Yields and reaction times obtained without catalyst and in the presence of MAP, DAP, TSP and TiP₂O₇ catalysts in case of the quinazolin-4(3H)-ones^a synthesis.

Entry	Catalyst	Time (min)	Amount of product (g)	Yield (%) ^b
1	-	600	trace	trace
2	TiP ₂ O ₇	30	0.216	84
3	MAP	90	0.219	85
4	DAP	80	0.214	83
5	TSP	60	0.229	89

^a Reaction conditions: anthranilamide (1 mmol), 4-chlorobenzaldehyde (1 mmol), DMF (3 mL), 10 mg mass of catalyst. ^b Isolated yields

From the results reported in Table 1, it can be noticed that the use of phosphate supports as catalysts decrease the reaction time and increase the product yield. Therefore, their application contributes to the development of green chemistry. The results obtained by TiP₂O₇, compared to those obtained by the MAP, DAP, and TSP, clearly show an appreciable time-saving. Indeed, after only 30 minutes, the yield of the desired product in the presence of TiP₂O₇ reaches 84%.

The optimal conditions of quinazolin-4(3H)-ones synthesis in the presence of the four catalysts (MAP, DAP, TSP, and TiP₂O₇) was determined. The effect of the solvent nature, its volume, and the catalyst amount were also examined. The effect of solvent nature was the first studied parameter. For this, the model reaction was carried out in the presence of different solvents such as polar aprotic (DMF, DMSO, EtOAc) and apolar solvents (dioxane, toluene). The obtained results are grouped in Table 2.

Table 2. Solvent effect of quinazolin-4(3H)-ones^a synthesis.

Entry	Catalyst	Solvent	Time (min)	Amount of product (g)	Yield (%) ^b
1	MAP	DMF	90	0.219	85
2	DAP	DMF	80	0.214	83
3	TSP	DMF	60	0.229	89
4	TiP ₂ O ₇	DMF	30	0.216	84
5	MAP	DMSO	90	0.213	83
6	DAP	DMSO	80	0.206	80
7	TSP	DMSO	60	0.224	87
8	TiP ₂ O ₇	DMSO	30	0.211	82
9	MAP	Toluene	90	0.180	70
10	DAP	Toluene	80	0.175	68
11	TSP	Toluene	60	0.186	72
12	TiP ₂ O ₇	Toluene	30	0.191	74
13	MAP	Dioxane	90	0.170	66
14	DAP	Dioxane	80	0.157	61

15	TSP	Dioxane	60	0.173	67
16	TiP ₂ O ₇	Dioxane	30	0.182	70
17	MAP	EtOAc	90	0.198	77
18	DAP	EtOAc	80	0.187	72
19	TSP	EtOAc	60	0.193	75
20	TiP ₂ O ₇	EtOAc	30	0.202	78

^a Reaction conditions: anthranilamide (1 mmol), 4-chlorobenzaldehyde (1 mmol), solvent (3 mL), 10 mg mass of catalyst. ^b Isolated yields

The experimental results indicate that the best yields are obtained with DMF as a solvent. Indeed, the yields of the desired product (**3a**) achieve 85, 83, 89, and 84% respectively for MAP, DAP, TSP, and TiP₂O₇. The reaction in DMSO and EtOAc led to the product (**3a**) with average yields, and in the case of dioxane and toluene, modest yields are observed.

One can deduce that the DMF is the appropriate solvent for quinazolin-4(3H)-ones synthesis. Therefore, it was chosen as a solvent of the studied reaction in the following part of this present work.

In the concept of green chemistry-based on minimizing the use of solvent, the reaction has been carried out in different volumes of DMF to study its influence on reaction time and product yield.

Table 3. Solvent volume influence on the quinazolin-4(3H)-ones ^a synthesis.

Entry	Volume	Time (min) / Amount of product (g) / Yield (%) ^b			
		MAP	DAP	TSP	TiP ₂ O ₇
1	1mL	90 / 0.231 / 89	80 / 0.218 / 84	60 / 0.233 / 90	30 / 0.225 / 87
2	2mL	90 / 0.227 / 88	80 / 0.215 / 83	60 / 0.231 / 90	30 / 0.220 / 85
3	3mL	90 / 0.219 / 85	80 / 0.214 / 83	60 / 0.229 / 89	30 / 0.217 / 84
4	4mL	90 / 0.205 / 80	80 / 0.199 / 77	60 / 0.213 / 83	30 / 0.208 / 81
5	5mL	90 / 0.191 / 74	80 / 0.190 / 73	60 / 0.201 / 78	30 / 0.196 / 76

^a Reaction conditions: anthranilamide (1 mmol), 4-chlorobenzaldehyde (1 mmol), DMF (x mL), 10 mg mass of catalyst. ^b Isolated yields

Table 3 shows that the good yields are obtained using 1 mL of DMF. A decrease in the yield of the reaction is observed when the volume increases. This can be explained by the formation of a solvent layer on the catalyst surface, which deactivating the interaction between the reagents and the catalyst. Consequently, the synthesis of quinazolin-4(3H)-ones can be carried

out in 1 mL of DMF, which corresponds perfectly to the principles of green chemistry.

To optimize the amount of each catalyst MAP, DAP, TSP or TiP₂O₇, the model reaction was realized by varying the mass of catalyst between 1 and 10 mg. The results are regrouped in Table 4.

Table 4. Catalyst amount optimization for the quinazolin-4(3H)-ones ^a synthesis.

Entry	Amount of catalyst (mg/mol %)				Time (min) / Amount of product (g) / Yield (%) ^b			
	MAP	DAP	TSP	TiP ₂ O ₇	MAP	DAP	TSP	TiP ₂ O ₇
1	1/0.8	1/0.7	1/0.4	1/0.5	90/0.227/88	80/0.232/90	60/0.225/87	30/0.219/85
2	2/1.7	2/1.5	2/0.8	2/0.9	90/0.236/91	80/0.237/92	60/0.229/89	30/0.227/88
3	3/2.6	3/2.3	3/1.2	3/1.3	90/0.239/93	80/0.242/94	60/0.233/90	30/0.232/90
4	4/3.3	4/3.1	4/1.7	4/1.8	90/0.244/95	80/0.241/93	60/0.236/92	30/0.242/94
5	5/3.5	5/3.8	5/2.2	5/2.2	90/0.242/94	80/0.236/91	60/0.239/93	30/0.241/93
6	6/5.2	6/4.6	6/2.6	6/2.7	90/0.240/93	80/0.233/90	60/0.247/96	30/0.236/91
7	7/6.1	7/5.3	7/2.9	7/3.1	90/0.235/91	80/0.227/88	60/0.244/95	30/0.233/90
8	8/6.9	8/6.1	8/3.4	8/3.6	90/0.233/90	80/0.225/87	60/0.240/93	30/0.229/89

9	9/7.8	9/6.8	9/3.9	9/4.1	90/0.231/89	80/0.220/85	60/0.235/91	30/0.227/88
10	10/8.5	10/7.6	10/4.3	10/4.5	90/0.229/89	80/0.218/84	60/0.233/90	30/0.225/87

^a Reaction conditions: anthranilamide (1 mmol), 4-chlorobenzaldehyde (1 mmol), DMF(1 mL), X mg mass of catalyst. ^b Isolated yields

The results show that the good yields were obtained when 4 mg of MAP or TiP_2O_7 , 3 mg of DAP, and 6 mg of TSP were used. For higher catalyst amounts, it is remarkable that the yield decreases, which can be explained by the dispersion of the reagents at the surface of the catalyst. These results are interesting because it takes into account the green chemistry principals that consist of minimizing the risk accompanied by the use of large quantities of catalyst.

One of the most critical points in green chemistry is the ability to reuse catalysts several times without losing its catalytic activity. For this, the reuse capacity of the used catalysts (MAP, DAP, TSP, and TiP_2O_7) was evaluated in the Synthesis of quinazolin-4(3H)-ones. Indeed, the model reaction was carried out several times under optimal conditions. The obtained yield was determined after each cycle of reuse. The results are shown in Figure 6.

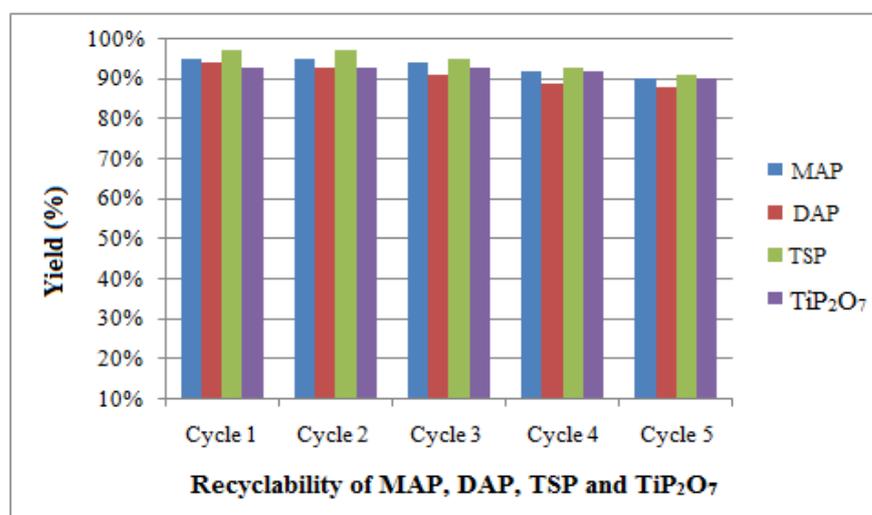


Figure 6. Recyclability of catalysts MAP, DAP, TSP, and TiP_2O_7

Figure 6 shows that the yields remain unchanged according to the number of the regeneration cycle. Thus, one deduces that there is no loss of catalytic activity even after five uses. The structure of TiP_2O_7 after its reuse was examined by XRD and IR analyzes.

The XRD and IR spectra of the TiP_2O_7 recovered after the five cycles prove that the catalyst structure has not undergone any modification even after five reuses (Figure 7).

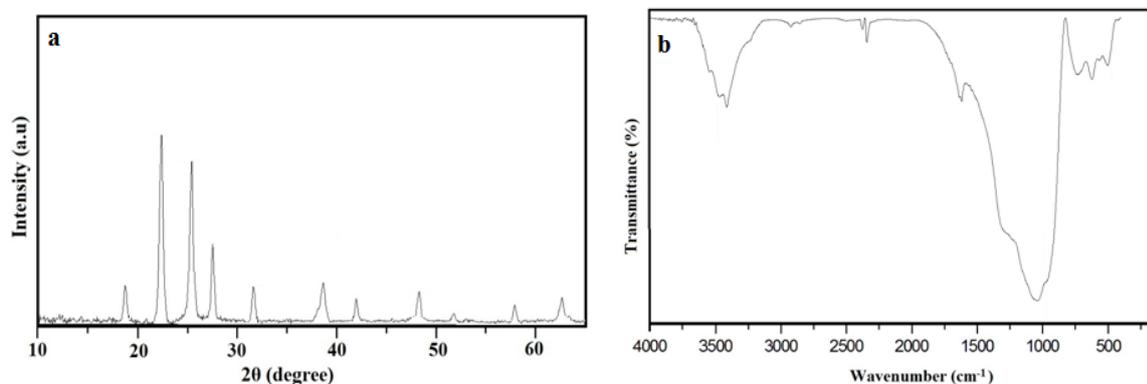


Figure 7. XRD analysis (a) and IR (b) for TiP_2O_7 after the last cycle of reuse

In order to examine the heterogeneity of TiP_2O_7 , a hot filtration test has been carried out using anthranilamide and 4-chlorobenzaldehyde under the optimized condition. After half time of the reactions

(Figure 8), the catalyst was separated from the reaction mixture, and the filtrate was allowed to continue the reaction under the same condition.

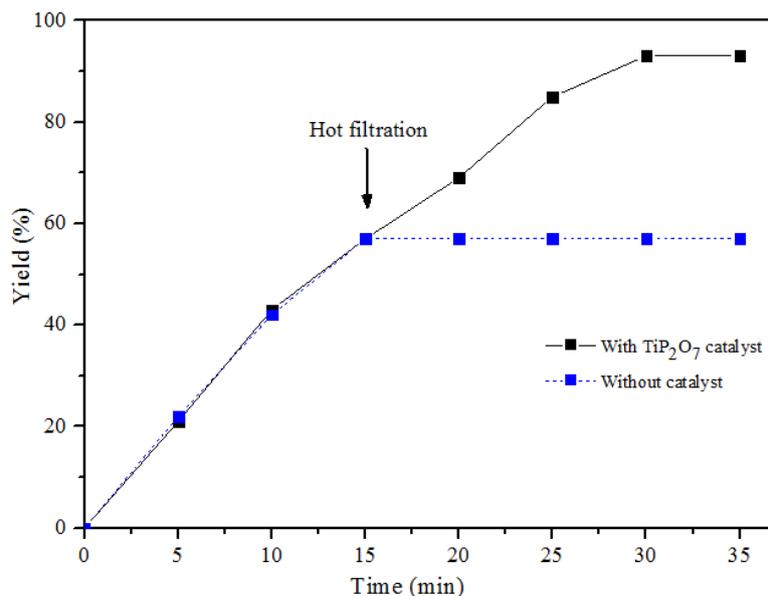
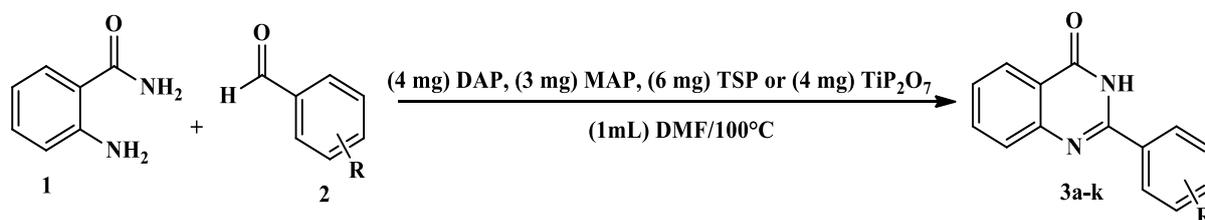


Figure 8. Heterogeneity test for the condensation of anthranilamide and 4-chlorobenzaldehyde

In half time, 57% of the product has been obtained. When the catalyst has been removed, any increase in the yield has been observed, indicating that Ti was not leached out from the catalyst into the solution. This implies that TiP_2O_7 is a heterogeneous catalyst.

After optimizing the operating conditions of quinazolin-4(3H)-one derivative Synthesis, they were applied for the generalization of the reaction. For this, various substituted aromatic aldehydes were employed (Scheme 2). Table 5 collects the results obtained for each aldehyde derivative.



Scheme 2. Synthesis of some quinazolin-4(3H)-ones

Table 5. Generalization of quinazolin-4(3H)-one synthesis.

Entry	R	Catalysts	Time (min) / Amount of product (g) / Yield (%)	TON	TOF (h^{-1})	mp ($^{\circ}\text{C}$) Found	mp ($^{\circ}\text{C}$) Reported
3a	4-Cl	MAP	90 / 0.244 / 95	27.29	18.19	>260	305–307 ⁶¹
		DAP	80 / 0.242 / 94	41.22	30.99		
		TSP	60 / 0.247 / 96	37.35	37.35		
		TiP_2O_7	30 / 0.242 / 94	51.38	102.76		
3b	4- NO_2	MAP	90 / 0.227 / 85	24.42	16.28	>260	363–364 ⁶¹
		DAP	80 / 0.224 / 88	38.59	29.01		
		TSP	60 / 0.229 / 86	33.20	33.20		
		TiP_2O_7	30 / 0.238 / 89	49.17	98.34		
3c	4- CH_3	MAP	90 / 0.189 / 80	22.98	15.32	236-237	236-239 ⁶²
		DAP	80 / 0.193 / 82	35.96	27.04		
		TSP	60 / 0.206 / 87	33.59	33.59		
		TiP_2O_7	30 / 0.199 / 84	46.40	92.80		
3d	4- $\text{N}(\text{CH}_3)_2$	MAP	90 / 0.223 / 84	24.13	16.09	241-242	240–242 ¹⁷

		DAP	80 / 0.239 / 90	39.47	29.67		
		TSP	60 / 0.233 / 88	33.97	33.97		
		TiP ₂ O ₇	30 / 0.236 / 89	49.17	98.34		
3e	H	MAP	90 / 0.193 / 87	25.00	16.66	239-240	239–241 ⁶²
		DAP	80 / 0.197 / 89	39.03	29.34		
		TSP	60 / 0.202 / 91	35.16	35.16		
		TiP ₂ O ₇	30 / 0.205 / 92	50.82	101.64		
3f	2-OH	MAP	90 / 0.215 / 90	25.86	17.24	>260	272–274 ⁶³
		DAP	80 / 0.205 / 86	37.71	28.36		
		TSP	60 / 0.211 / 89	34.36	34.36		
		TiP ₂ O ₇	30 / 0.216 / 90	49.72	994.4		
3g	4-OH,3-OCH ₃	MAP	90 / 0.225 / 84	24.13	16.08	238	238–240 ⁶³
		DAP	80 / 0.220 / 82	35.96	27.03		
		TSP	60 / 0.234 / 87	33.59	33.59		
		TiP ₂ O ₇	30 / 0.228 / 85	46.96	93.92		
3h	4-OMe	MAP	90 / 0.212 / 84	24.13	16.08	244	243-244 ¹⁸
		DAP	80 / 0.204 / 81	35.52	26.70		
		TSP	60 / 0.222 / 88	33.97	33.97		
		TiP ₂ O ₇	30 / 0.225 / 89	49.17	98.34		
3i	4-Br	MAP	90 / 0.261 / 87	25.00	16.66	198	197–199 ⁶¹
		DAP	80 / 0.253 / 84	36.84	27.69		
		TSP	60 / 0.271 / 90	34.74	34.74		
		TiP ₂ O ₇	30 / 0.280 / 93	51.38	102.76		
3j	4-OH	MAP	90 / 0.198 / 83	23.85	15.90	>260	>300 ¹⁷
		DAP	80 / 0.195 / 82	35.96	27.04		
		TSP	60 / 0.212 / 89	34.36	34.36		
		TiP ₂ O ₇	30 / 0.207 / 87	48.06	96.13		
3k	3,4-OMe	MAP	90 / 0.218 / 77	22.12	14.75	248	246-248 ⁶⁴
		DAP	80 / 0.226 / 80	35.08	26.38		
		TSP	60 / 0.240 / 85	32.81	32.81		
		TiP ₂ O ₇	30 / 0.252 / 89	49.17	98.28		

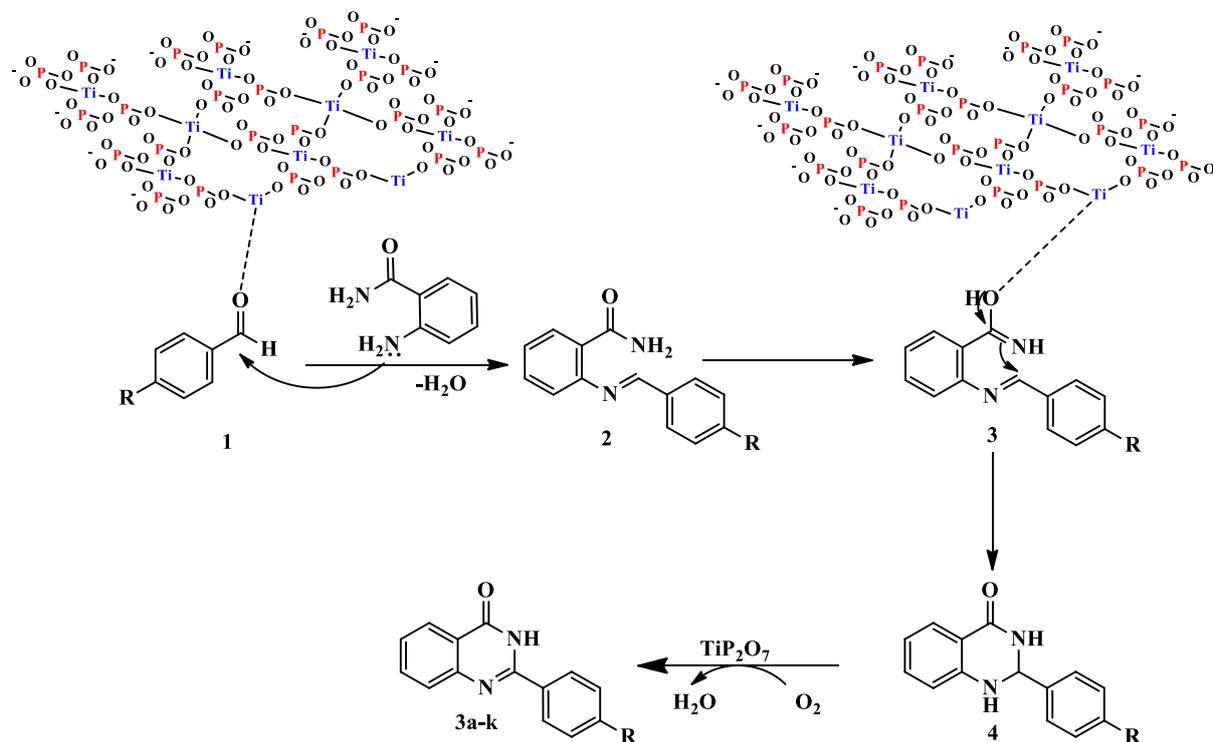
The results show that good to excellent yields of products with high values of TON and TOF are obtained by using a variety of aromatic aldehydes possessing different substituents. Indeed, the aromatic aldehydes with electron-donating groups (4-CH₃, 4-N(CH₃)₂, 2-OH, 4,3-OH, CH₃, 4-OCH₃, 3,4-OCH₃) give desired products with good yields (Table 5, entries **3c**, **3d**, **3f-3h**, **3j**, **3k**). The obtained yields are between 77 and 90% in reaction times varying between 30 and 90 minutes. When the aromatic aldehyde having an electron-withdrawing group (4-NO₂) is used, the reactions give the product **3b** with high yields (85 to 89%).

For the aldehyde having a halogen functionality (4-Cl, 4-Br), it is shown that reacted smoothly with anthranilamide to provide similar products **3a**, **3i** with excellent yields 84–96%.

These results show that whatever the aromatic aldehyde group, the yield remains excellent (≥ 77 %). Indeed, the catalytic activity of the used catalyst has not been affected by the nature group of aromatic aldehyde. Therefore, it can be deduced that TiP₂O₇ is an efficient catalyst for the quinazolin-4(3H)-ones synthesis.

The role of the titanium phosphate (TiP_2O_7) in the synthesis of quinazolin-4(3H)-one, may be explained by a suggested mechanism involving the condensation

of aromatic aldehyde and anthranilamide in the presence of TiP_2O_7 , which acts as a Lewis acid catalyst (Scheme 3).



Scheme 3. A plausible mechanism for the formation of quinazolin-4(3H)-ones

Le schéma 3 montre que la réaction commence avec l'action de l'anthranilamide et de l'aldéhyde en présence de TiP_2O_7 pour former l'intermédiaire 2. Ce dernier est activé par TiP_2O_7 facilitant l'attaque nucléophile intermoléculaire de l'azote sur le carbone imine, conduisant ainsi à l'intermédiaire 4. The latter then undergoes aerobic oxidation catalyzed by TiP_2O_7 to give the desired product **3a-k**. To improve

the experimental results, a comparison study between the catalytic activity of the used catalysts (MAP, DAP, TSP, and TiP_2O_7) and that of other catalysts reported previously for the same synthesis was necessarily developed. Table 6 presents the reaction conditions, the yields, and the reaction time for each catalyst.

Table 6. Comparison between some catalysts described in the literature and the catalysts used.

Entry	Catalyst	Reaction conditions	Time	Yield (%)
1	MAP	DMF/100°C	90 min	95
2	DAP	DMF/100°C	80 min	94
3	TSP	DMF/100°C	60 min	96
4	TiP_2O_7	DMF/100°C	30 min	93
5	$\text{Cu}_2\text{ZrO}_3 / \text{H}_2\text{O}_2$	EtOH/reflux	1.5 h	95 ⁶⁴
6	Cp_2ZrCl_2	DMF/100°C	4 h	82 ⁶⁵
7	CuCl_2	DMSO/120°C	24 h	72 ⁶⁶
8	$\text{Fe}(\text{NO}_3)_3 \cdot \text{H}_2\text{O}$	DMSO/120°C	24 h	80 ⁶⁶
9	$\text{VO}(\text{acac})_2$	DCE, air/80°C	6 h	84 ⁶⁷
10	$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$	EtOH/reflux	16 h	94 ⁶⁸
11	$\text{K}_4\text{Fe}(\text{CN})_6$	$\text{CH}_3\text{CN}/70^\circ\text{C}$	9 h	35 ¹⁸
12	$\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$	$\text{CH}_3\text{CN}/70^\circ\text{C}$	9 h	25 ¹⁸

The obtained results show that the MAP, DAP, TSP, and TiP_2O_7 are more efficient than other catalysts presented in Table 6. Indeed, their application led to obtaining a higher yield of products in short reaction time. While $\text{Cu}_2\text{ZrO}_3/\text{H}_2\text{O}_2$, CuCl_2 , Cp_2ZrCl_2 ,

4. Conclusion

To sum-up, an efficient and green method was developed for quinazolin-4(3H)-one derivatives synthesis, through the condensation of anthranilamide with 4-chlorobenzaldehyde using MAP, DAP, TSP, and TiP_2O_7 as heterogeneous catalysts. The products were obtained with excellent yields in short reaction time, which shows that these four catalysts have unusual catalytic activity. Also, these catalysts were reused at least five times without any loss of their efficiency. According to the comparison between the prepared titanium phosphate and the three phosphate fertilizers MAP, DAP, and TSP, TiP_2O_7 was considered as the most efficient catalyst for quinazolin-4(3H)-one derivatives synthesis. Indeed, the modification by TiCl_4 has improved the catalytic activity of the three phosphate fertilizers. Therefore, TiP_2O_7 can be considered as an efficient catalyst for other organic syntheses, and its application can contribute to green chemistry development.

$\text{K}_4\text{Fe}(\text{CN})_6$, $\text{Fe}(\text{NO}_3)_3 \cdot \text{H}_2\text{O}$, $\text{VO}(\text{acac})_2$, $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$ and $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ gives lower yields in long reaction times. Besides, some of these catalysts are non-recyclable, which presents a real environmental problem

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