International Journal of Universal Science and Technology
ISSN: **ISSN: 2454-7263** Copyright © Universal Print
Volume No. 03, Issue No. 04, Page No. 206-210 Published: Jan. 2018
Web: www.universalprint.org , Email: ijup@universalprint.org
Title Key: Synthesis of 2- Substituted-3-(Phenylamino)-…

Synthesis of 2- Substituted-3-(Phenylamino)-Dihydroquinazoline-4(1H)-Derivatives by Using Titanium Dioxide as A catalyst

Pandey Archana S., Kongi Ankita R., Shaikh Saba S. Khandebharad Amol U., Sarda Swapnil R.

Department of Chemistry, J. E. S. College, Jalna,(MS) INDIA.

Email: srsarda@rediff.com

Abstract

An environmentally friendly method developed for the synthesis of pharmaceutically significant 2-substituted-3-(phenylamino)-dihydroquinazoline-4(1H)-derivatives by three component condensation of aromatic aldehyde, Isatoic anhydride and phenyl hydrazine in presence of Titanium dioxide(TiO_2) at reflux condensation in alcohol as a solvent**.** The present study shows that TiO_2 is the heterogeneous catalyst and found to be the green and effective catalyst. Major highlights of this method includes higher product yields in a short reaction time and simple workup procedure

Keywords: Multicomponent reaction (MCR); Isatoic anhydride; Aromatic aldehyde; Phenylhydrazine; 2- substituted-3-(phenylamino)-dihydroquinazoline-4(1H)-derivatives.

1. Introduction

In past few years, major attention has been focused on developing sustainable methods using green chemistry principles[1].The fascinating area of development in this regard is the use of safer non-volatile solvents. Avoid of traditional solvents, environmental compatibility, safe handling, easy availability of starting materials non-toxicity, and inflammability [2,3]. One-pot transformations, particularly multi-componentreactions (MCRs) are of great interest to organic chemists [4].The multi-component reactions have been used in order to focus on the design and advancement of environmentally friendly and less expensive methods for the generation of libraries of heterocyclic compounds. Therefore, academic and industrial research groups have focused more on the development of MCRs so as to invent new, efficient, synthetic methodologies to afford vast variety ofbiologically-active compounds [6].

A literature survey describes the valuable physiological properties of mono anddisubstituted 2,3-dihydroquinazoline-4(1H)-ones derivatives, which includes kinase inhibition,anticancer, antimalarial, anticonvulsant, antifertility, antibacterial,and antifungal properties [6-12]. It also shown the neurodegenerativeimpartments[13], neuron-protective effects of a novel poly-(ADP-ribose)-polymerase-1inhibitor[14].The recent method offers the several advantage dignified in short reaction time eco-friendly reaction media and recapituable catalyst. All the synthesised of 2- substituted-3-(phenylamino)-

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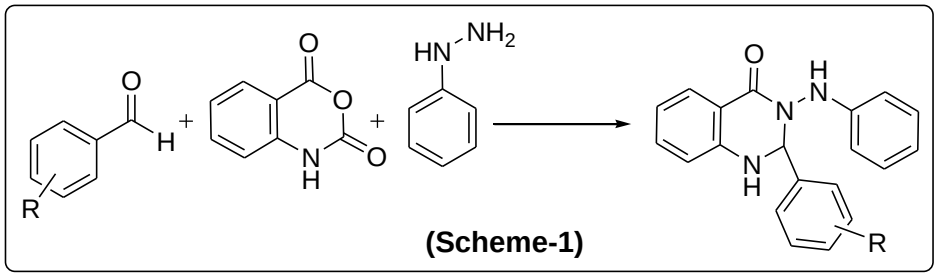
dihydroquinazoline-4(1H)-ones were screened for antibacterial activity against *E.coli*.

These above mentions properties of quinazoline make it as interesting structure so that several methods are available for the synthesis and evaluation of their analogy heterocycles. diverse protocols have been applied for the synthesis of quinazoline derivatives[15,16]. Among the derivatives of quinazoline 2-Substituted-3-(phenylamino)-dihydroquinazolin-4 (1H)-ones got the more biological interest.

The extensive literature is available on the synthesis of quinazolinones using diverse protocols [17-20]. The most common strategy includes the multicomponent reaction of isatoic anhydride, amines/amino salts, and aldehydes. Dabiri et al. have demonstrated various routes to construct quinazolinone [21, 22]. Moreover, a variety of catalytic systems such as nano particles of Fe_3O_4 [23], ZnO [24], $Ga(OTf)_3$ [25], Amberlyst-15 [26], and $Zn(PFO)_2$, have been adopted for the synthesis of quinazolinone derivatives.

However, most of these methods have serious drawbacks such as the use of toxic and expensive catalysts, use of hazardous volatile solvents, low yields, and longer reaction times. There is need to develop a new for the synthesisof quinazolinone derivatives.

In continuation of our interest in the application of ecofriendly methods in organic synthesis [27], and in view of assembling new structures througha diversity-oriented approach, we report herein the one-pot multicomponent synthesis of 2-substituted-3-(phenylamino)-dihydroquinazoline-4(1H)-derivatives following green chemistry principles (Scheme-1).



(Scheme-1)

2. General procedure for the 2-substituted-3-(phenylamino)-dihydroquinazoline-4(1H)-derivatives

A mixture of benzaldehydes (1 mmol) with Isatoic anhydride (1 mmol) and phenylhydrazine /ammonium carbonate/aniline(1 mmol) was stirred in 15 ml of ethanol containing TiO_2 (20 mol %) at reflux temperature for a certain period of time (**Table-4**). The progress of reaction monitored by TLC by using n-hexane: ethyl acetate (8:2). After completion of reaction , the resulting crude product was poured onto crushed ice and the solid product was filtered off and recrystallized in absolute ethanol to get the corresponding pure product.

Spectral data of selected compounds:

2-Phenyl-3-(phenylamino)-2,3-dihydro-2-phenylquinazolin-4(1*H*)-one(entry 1): **^{1}H NMR (300 MHz, $CDCl_3$):** δ 5.96 (s, 1H, CH), 6.65 (d, J=9 Hz, 1H, HAr), 6.85 (s, 1H, NH), 6.86-6.97 (m, 4H, HAr), 7.22-7.28 (m, 2H, HAr), 7.31-7.42 (m, 7H, HAr), 7.94 (d, J=1.5 Hz, 1H, NH) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** :δ 74.9, 113.9, 114.3, 114.5, 119.2, 121.5, 126.4, 128.7, 128.8, 129.2, 129.3, 134.2, 139.4, 145.6, 146.4, 163.6 ppm; **HR-MS (ESI): m/z**: 316.1472 [M+H]+.

3. Result and discussion

In order to optimize the reaction conditions,we have chosen the reactionof benzaldehyde(1 mmol), isatoic anhydride (1 mmol) and pheylhydrazine (1 mmol) as a standard model reaction. Initially the effect of various catalystwas studied by taking ethanol

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as a solvent at reflux condition which is summarized in Table-1. The results indicated that catalyst had a significant effect on the product yield. according to the literature survey it has become outward that formation of 2- substituted-3-(phenylamino)-dihydroquinazoline-4(1H)-derivatives does not takes place in absence of catalyst this clarified the need of catalystin an order to evaluate the effect of catalyst the various catalyst were used for performing the model reaction. The oxides of metals and non-metals were utilised for this purpose it was observe that reaction proceeds smoothly in presence of TiO_2 (Table-1, entry 5). Other catalystlike MgO and Al_2O_3 also gave moderate amount of yield but required long reaction time.

Table-1: Optimisation of catalyst[a]:

Entry	Catalyst	Time(hrs)	Yield[b](%)
1	SiO_2	4	60
2	Al_2O_3	3	70
3	CeO_2	6	67
4	MgO	2	84
5	TiO_2	1	90

[a]**Reaction condition:** Benzaldehyde (1mmol); Isatoic anhydride (1mmol); Phenyl hydrazine (1mmol) and catalyst 20 mol % in 10 ml Ethanol stirred at reflux condensation.
[b] **Isolated yield**

Further to know the precise role of solvent model reaction was performed under solvent free condition at reflux temperature to our surprised, reaction in neat condition was observed to result with 50% yield as the selection of an solvent is of crucial important for the success of reaction reaction was screened by various solvent in presence of TiO_2. The results shows that the effectiveness of solvents on the product yield. The use of Tulane actetonitrile and n-hexane give the poor yield. Solvents like DMF methanol ethanol gave moderate yields. The best conversions obtain in methanol based on this results ethanol was selected as the medium for further investigation.

Table-2: Optimisation of solvent[a]

Entry	Catalyst	Time (hr.)	Yield(%)
1	Neat	5	50
2	MeOH	2	82
3	DMF	3	78
4	Toulene	5	30
5	Acetonirile	4	45
6	n-hexane	5	25
7	**EtOH**	**1**	**90**

[a]**Reaction conditio**n: Benzaldehyde (1mmol); Isatoic anhydride (1mmol); Phenyl hydrazine (1mmol) and catalyst titanium dioxide (20 mol %) in 15 ml of solvent stirred at reflux condensation.
[b]**Isoalted yield:**

In order to establish the appropriate quantity of ethanol, the model reaction was investigated 15 ml of ethanol yielding the desired product in 90 % respectively.Which conclude that 15ml of solvent is sufficient quantity to carry out the reaction efficiently. To evaluate the appropriate temperature we carried out the model reaction at RT 60°C,80°C and reflux condition (Table-3). However increasing the temperature enhances the reaction rate substantially with respective 40%,62%,70% and 90% respectively.to evaluate the appropriate concentration of catalyst model reaction was investigated by taking 10,15,20 mole % of catalyst. The product was formed in 60%,72%and 90% yield respectively (Table-3, entry).

With this satisfactory result it was finalise that 20 mole % of TiO_2 in 10ml of ethanol as solvent at reflux temperature is the optimised reaction condition to generalise the effect of catalyst for different aldehyde.

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Table-3:Optimisation of temperature[a]

Entry	Temperature	Quantity %	Yield[b] %
1	RT	20	40
2	60	20	62
3	80	20	70
4	reflux	20	90
5	reflux	10	60
6	reflux	15	72
7	**reflux**	**20**	**90**

[a]**Reaction condition:** Benzaldehyde (1mmol); Isatoic anhydride (1mmol); Phenyl hydrazine (1mmol) and catalyst titanium dioxide in 10 ml of solvent stirred.
[b]**Isoalted yield**

The key advantage of present protocol is associated with recyclability of the catalyst the catalyst was separated from the reaction mixture by simple filtration followed by washing with ethanol and heated up to 150°C the same catalyst was used for the present reaction repeatedly which is in good agreement to reuse the catalyst up to four cycles this result showed that the catalyst had no significant change in activity.

Table-4: Synthesis of 2-substituted-3-(phenylamino)-dihydroquinazoline-4(1H) [a]

Sr. no.	R_1	hydrazine	yield[b]	Time (min)	mp°C
1	Ph	$PhNHNH_2$	90	60	201
2.	4-OMe- Ph	$PhNHNH_2$	80	50	183
3.	2-OH- Ph	$PhNHNH_2$	78	75	191
4.	4-Me- Ph	$PhNHNH_2$	80	90	161
5.	4-NO_2-Ph	$PhNHNH_2$	80	60	222
6.	Ph	4-Me - $PhNH_2$	90	50	193
7.	4-NO_2-Ph	4-Me - $PhNH_2$	85	60	213

[a]**Reaction Conditions:** Aromatic aldehyde (1mmol),isatoic anhydride (1mmol), hydrazine (1mmol) and TiO_2 catalyst (20 mol%) in 15 ml of ethanol at reflux temperature.
[b]**Isolated yields**

4. Conclusion

In summary, we reported a simple, eco-friendly, one pot three-component reaction for the synthesis 2- substituted-3-(phenylamino)-dihydroquinazoline-4(1H)- derivatives. This protocol offers several advantages such as atom economy, short reaction time, simple work-up and mild reaction condition. Moreover catalyst was reused for several runs with an insignificant loss of activity.

5. Acknowledgments

The Authors are thankful to the principal Dr. J.D.Kabara, J.E.S. College for providing laboratory facilities and his kind support in the completion of this work.

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