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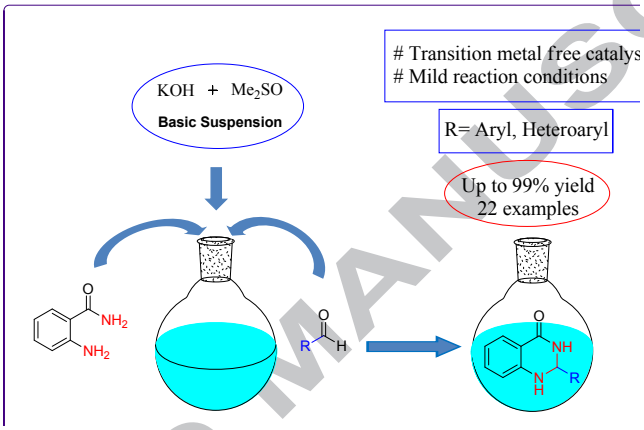

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KOH/DMSO: A Basic Suspension for Transition Metal-Free Tandem Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones

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ABSTRACT

A novel protocol for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from 2-aminobenzamides and aldehyde derivatives catalyzed by KOH/DMSO suspension has been developed. The present transition metal free methodology is operationally simple, scalable and varieties of 2,3-dihydroquinazolin-4(1*H*)-one derivatives were obtained in good to excellent yields in short reaction times.

Introduction

In the last few decades, synthesis of valuable organic molecules by using principles of green chemistry has become more demanding and interesting for organic chemists. Reactions which proceed via green reaction medium in the absence of expensive reagents and hazardous chemicals as well as produce minimum waste are considered as ideal reactions.[1] In organic synthesis, transition metal free protocols are considered as more economical than metal mediated reactions as the latter has many disadvantages such as high cost of metal catalysts, possibility of metal contamination in final products etc. Hence, an enormous number[2] of transition metal-free approaches have been developed over the past decades and chemists are now focusing on this area to develop more advantageous methods than the existing ones.

Nitrogen containing heterocycles are found in a plethora of biological active molecules including natural products. Among the N-containing heterocyclic molecules quinazolinone scaffold is a core element of many pharmaceutically active compounds. Many quinazolinone motifs possess broad range of biological and therapeutic activities such as antimalarial,[3] anticancer,[4] antitumor,[5] antitubercular,[6] anti-HIV,[7] anti-inflammatory,[8] antiviral,[9] antihypertensive,[10] and anticonvulsant.[11] Therefore, tremendous efforts have been projected to discover simple and direct approaches towards the synthesis of quinazolinone nucleus. There are many approaches available for the synthesis of these biologically essential quinazolinones,[12-14] among them one of the most popular methods is the cyclocondensation of 2-aminobenzamide with carbonyl analogues. Recently different strategies were developed for the synthesis of quinazolinones by employing different types of acid catalysts as well as transition metal based catalysts such as sulfamic acid,[15] zirconium chloride,[16] $Sc(OTf)_3$,[17] NH_4Cl,[18] p-TsOH,[19] $CuCl_2$,[20] and $[Bmim]PF_6$.[21] Although these methods are very useful but some of them have limitations such as harsh reaction conditions, use of expensive reagents, long reaction time and tedious work-up procedures. Literature revealed that this reaction is mainly carried out in presence of acid catalyst but in 2014, O. Obaiah *et al.* developed a methodology for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using basic ionic liquid[22] as a catalyst. To the best of our knowledge, this is the only report of base catalyzed quinazolinone synthesis from 2-aminobenzamide and carbonyl compounds. Therefore, developing new basic catalytic systems for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from 2-aminobenzamide and carbonyls is expected to gain a lot of interest among scientific community.

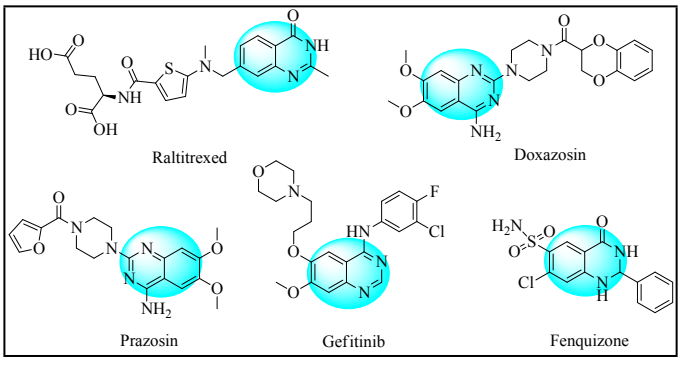


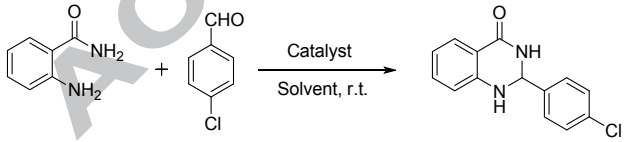
Figure 1: Quinazoline containing drug molecules.

Herein, we have described the results of our systematic study to elaborate a practical and scalable synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using KOH/DMSO suspension at room temperature.

Results and discussion

Our aim was to show the versatile catalysis of our previously reported CuNPs/NC catalyst[23] in 2,3-dihydroquinazolin-4(1*H*)-ones synthesis since literature revealed that synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones proceeds faster in the presence of copper source as catalyst. Therefore, we initially performed the reaction in the presence of CuNPs/NC catalyst taking 2-aminobenzamide and 4-chlorobenzaldehyde as model substrate. The reaction was carried out at room temperature in different solvents but after 24 hours only a trace amount of product was obtained when DMSO was chosen as solvent (**Table 1**, entry 1). Then we carried out the same reaction in presence of different types of bases (**Table 1**, entries 2-5). To our delight the yield of the product was maximum in presence of KOH along with copper catalyst which gives quantitative yields of product within 30 minutes (**Table 1**, entry 5). To justify the role of copper, we performed a reaction without using copper catalyst; unexpectedly we observed that our desired product was obtained within 30 minutes with 99% yields of product (**Table 1**, entry 6). This accidental finding encouraged us to proceed further without copper catalyst. Then we screened different types of inorganic bases and among them Cs_2CO_3 and NaOH give good yields of products but Cs_2CO_3 takes longer period of times and NaOH gives slightly lower yields of product than KOH. We also screened some organic bases, ionic liquids as well as some basic water extract of waste materials but no one gave better results than KOH. After choosing the best base KOH, different types of solvents were used to check the solvent effects. Water miscible solvents like DMSO, DMF and DMA (dimethyl acetamide) give higher yields of product in short reaction time. We have also performed the reaction in presence of water but it takes longer times for higher yields of product. Among the solvents we have screened, DMSO was found to the best in terms of product yields and reaction time (**Table 1**, entry 6). Further to optimized the amounts of KOH different molar solutions of KOH in water were prepared and 2 mL of those solutions were used for the reaction along with DMSO as solvent and it was found that 0.2 M KOH solution (**Table 1**, entry 23) gives same result as obtained with using 1 mmol of KOH**.**

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (mg)	Base	Solvent	Time (h)	Yield[b] (%)
		Effect of Catalyst			
1	CuNPs/NC (20)	-	DMSO	24	20
2	CuNPs/NC (20)	K_2CO_3 (1 mmol)	DMSO	24	30
3	CuNPs/NC (20)	Ca_2CO_3 (1 mmol)	DMSO	24	30
4	CuNPs/NC (20)	Cs_2CO_3 (1 mmol)	DMSO	9	90
5	CuNPs/NC (20)	KOH (1 mmol)	DMSO	30 min	99
		Effect of Basic Catalyst			
6	-	KOH (1 mmol)	DMSO	30 min	99
7	-	NaOH (1 mmol)	DMSO	30 min	75
8	-	K_2CO_3 (1 mmol)	DMSO	30 min	00
9	-	Cs_2CO_3 (1 mmol)	DMSO	7	70
10[c]	-	ESP (20 mg)	DMSO	10	00
11[d]	-	WEB (2 ml)	DMSO	10	00
12	-	[OMIM]OH (2 ml)	-	3	00
13	-	DABCO (1 mmol)	DMSO	3	10
14	-	Et_3N (1 mmol)	DMSO	3	20
		Effect of Solvent			
15[e]	-	KOH (1 mmol)	EG	3	45
16	-	KOH (1 mmol)	EtOH	10	50
17	-	KOH (1 mmol)	H_2O	3	50
18	-	KOH (1 mmol)	DMF	20 min	85
19	-	KOH (1 mmol)	DMA	20 min	90
		Effect of Concentration of KOH			
20	-	KOH (0.01M)	-	30 min	10
21	-	KOH (0.01M)	DMSO	30 min	25
22	-	KOH (0.1M)	DMSO	30 min	85
23	**-**	**KOH (0.2M, 0.4 mmol)**	**DMSO**	**30 min**	**95**
24	-	KOH (0.2M)	DMF	30 min	30
25	-	KOH (0.2M)	DMA	30 min	75
26	-	KOH (0.3M)	DMSO	30 min	95

[a]Reaction conditions: 2-Aminobezamide (1 mmol), 4-chlorobenzaldehyde (1.2 mmol) and others stated in the table were stirred at room temperature.

[b]Isolated yield.

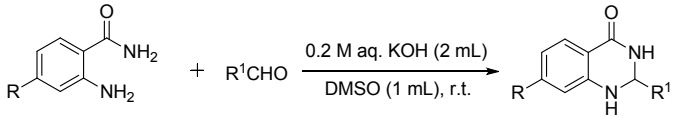
[c]ESP: Egg shell powder.

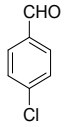
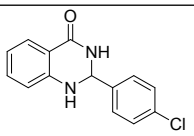
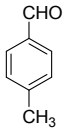
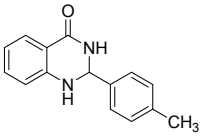
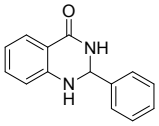
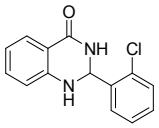
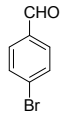
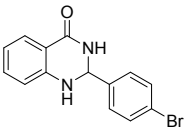
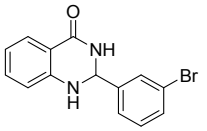
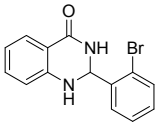
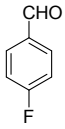
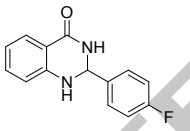
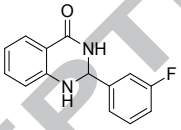
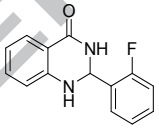
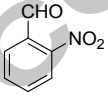
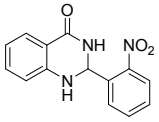
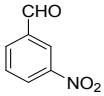
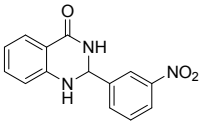
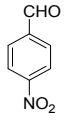
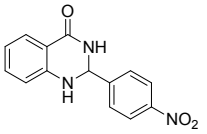
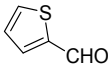
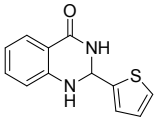
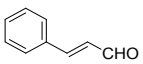
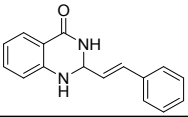
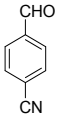
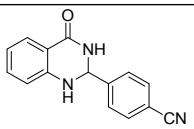
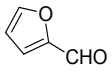
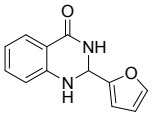
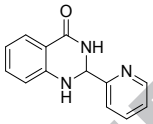
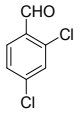
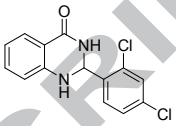
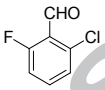
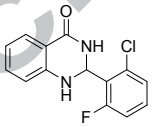
[d]WEB: Water extract of banana.

[e]EG: Ethylene glycol.

Encouraged by these results, various 2,3-dihydroquinazolin-4(1*H*)-ones were synthesized by using KOH/DMSO basic medium to investigate the scope and generality of our catalytic system. As shown in **Table 2**, all the aldehydes examined provided good to excellent yields of products. It was found that the aldehydes containing halides as substituent react faster with 2-aminobenzamide and give the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones within very short reaction time (**Table 2**, entries 1,4-10,19,20). Heterocylic aldehydes were also condensed with 2-aminobenzamide successfully and the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones were obtained in good yields at short reaction times (**Table 2**, entries 17,18).

Table 2 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones[a]



Entry	R	Aldehydes	Products	Time (min)	Yield[b] (%)
1	H			30	95
2	H			120	90
3	H			120	85
4	H			15	99
5	H			15	97
6	H			10	98
7	H			10	99
8	H			15	96
9	H			15	95
10	H			15	93
11	H			30	95
12	H			90	90
13	H			45	90
14	H			60	95
15	H			30	95
16	H			15	95
17	H			180	80
18	H			35	95
19	H			60	80
20	H			60	95
21	H			180	NR
22	H			180	NR
23	Cl			180, 90	45, 90[c]
24	Cl			120, 45	50, 95[c]

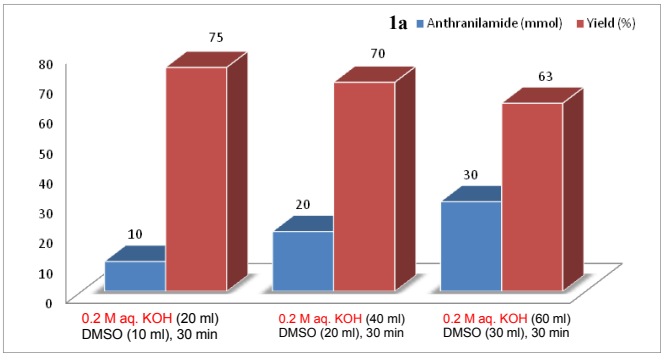
[a]Reaction conditions: 2-Aminobezamides (1 mmol), substituted aldehydes (1.2 mmol), 0.2 M aq. KOH (2 mL, 0.4 mmol) in DMSO (1 mL) was stirred at room temperature. NR: No reaction

[b]Isolated Yield.

[c]KOH (0.4 mmol) in DMSO (1 mL) at room temperature.

To demonstrate the synthetic utility of this protocol, three gram-scale reactions were carried out by using the substrates **1a** (1.36 g, 10 mmol) with **1b** (1.69 g, 12 mmol), **1a** (2.72 g, 20 mmol) with **1b** (3.37 g, 24 mmol) and **1a** (4.08 g, 30 mmol) with **1b** (5.06 g, 36 mmol) under the standard reaction conditions. As per our expectation, reactions give the corresponding product **2a** in good yields (75%, 70% and 63% isolated yields respectively). The graphical representations of the results are shown in **Scheme 1**.

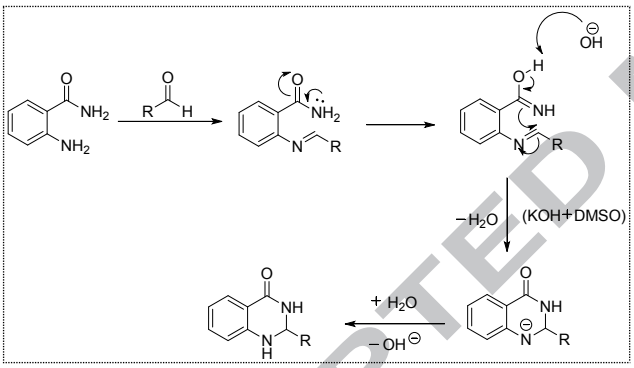
1a **1b** **2a**



Scheme 1: Gram scale synthesis

Plausible mechanism of the reaction:

Based on the above results, a plausible reaction mechanism has been proposed for this protocol (Scheme 2). The reaction was initiated with the formation of Schiff base intermediate between aldehyde and 2-aminobezamide in the presence of KOH/DMSO suspension. Then delocalisaztion of the lone-pair on nitrogen atom to the elctrophilic carbon atom followed by the abstraction of the proton by the hydroxide ion of the KOH/DMSO suspension resulted in the formation of cyclized product with a negative centre on nitrogen atom. Finally, protonation takes place from the water molecule which was released in the previous step and give the desired 2,3-dihydroquinazolin-4(1*H*)-one.



Scheme 2: Plausible reaction mechanism

Conclusion

In summary, we have succeeded in developing a simple and eco-friendly methodology for synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones catalyzed by KOH/DMSO suspension at room temperature. With the ease of procedure, the use of easily accessible and inexpensive substrates, short reaction times and utility for the synthesis of a wide range of derivatives made this protocol very attractive. We believe that this greener and cost effective process finds application in the synthesis of quinazolinone containing pharmaceutical compounds.

Acknowledgments

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24. Typical experimental procedure: 2-Aminobezamides (1 mmol) and substituted aldehyde (1.2 mmol) and 0.2 M solution of KOH in water (2 mL) in DMSO (1 mL) were stirred at room temperature. The progress of the reaction was monitored by TLC under UV light. After completion of the reaction the mixture was extracted with ethyl acetate (3 x 10 mL) and washed with water (3 x 10 mL). The combined extract was dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure. The product was purified by column chromatography over silica gel using n-hexane/ethyl acetate (3:1 v/v) as eluent to get the purified product. The products were then characterized by ESI-MS, ^{1}H NMR and ^{13}C NMR spectra.

Supplementary Material

General Information, Experimental and Analytical data, ^{1}H and ^{13}C NMR spectra and characterisation data of all the synthesised compounds are available as Supplementary Information

KOH/DMSO: A Basic Suspension for Transition Metal-Free Tandem Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones

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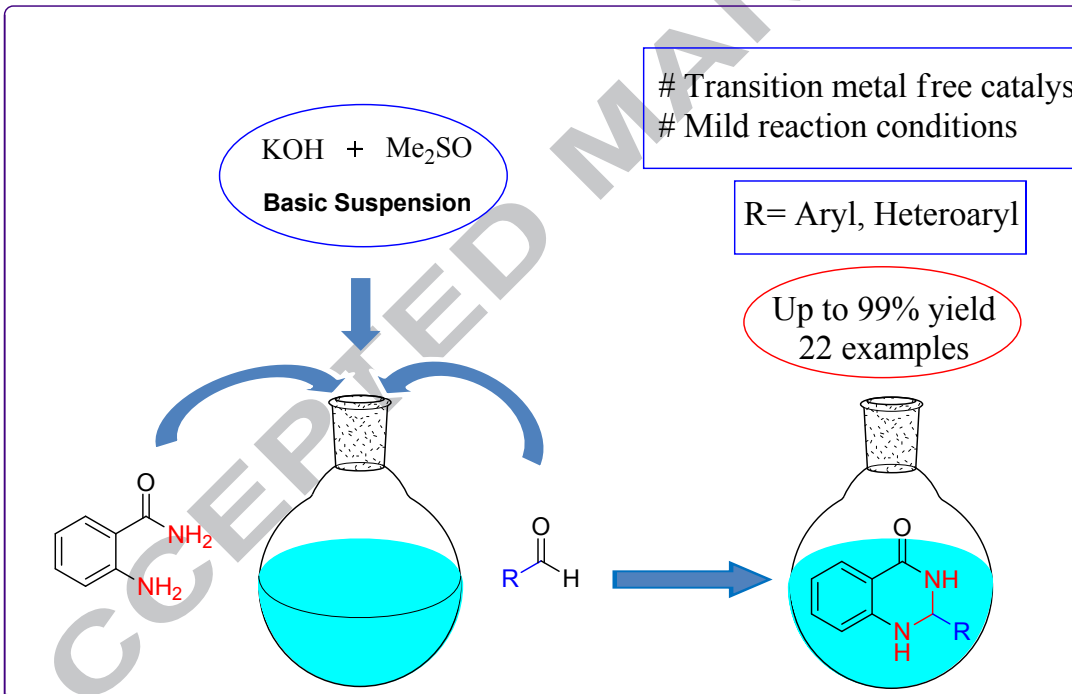

Highlights:

- Transition metal free catalyst is the major advantage of the present strategy.
- Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using basic suspension as catalyst.
- Scalable synthesis of the method is important from industrial perspective.
- Broad substrate scope of products with good to excellent yields.