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An Efficient and Facile Multi-component Synthesis of Quinazolin-2-(1*H*)-one/thione Derivatives

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Abstract

The Cerric Ammonium Nitrate catalyst was used and found to be effective for the efficient and facile synthesis of functionalized Quinazolin-2-(1*H*) Derivatives. The reaction system here gives Quinazolin-2-(1*H*) derivatives in moderate to high yields in reasonable reaction times. The high atom economy, high yield, mild reaction conditions and low reaction time are some of the important features of this protocol.

1. Introduction

Quinazoline and its synthetic analogues have been found to exhibit a broad spectrum of activity such as antibacterial[1], antimicrobial[2], analgesic[3] and anti-helmintic[iv]. Thus there has been considerable interest in the chemistry of quinazoline and its synthetic analogues in recent years.

In recent years, multi-component reactions (MCR's) have gained wide applicability in the field of synthetic organic chemistry as they increase the efficiency of the reaction and decrease the number of laboratory operations along with quantities of solvent and chemicals used. The development of new and efficient synthetic methodologies for the rapid construction of potentially bioactive compounds constitutes a major challenge for chemists in organic synthesis. MCRs are very useful to generate diverse combinatorial libraries for drug discovery.[5-8]

One-pot multi-component reactions have attracted significant attention in organic and medicinal chemistry. In these reactions, highly diverse and complex compounds are produced from easily available precursors in a single step by formation of multiple new bonds in one pot. Thus, multi-component reactions are known as important and environmentally benign processes in synthetic chemistry because they decrease the number of steps and reduce energy consumption and waste production.

In the literature there are many reports found having one or more disadvantages therefore we studied synthesis of 8-benzylidene-3,4,5,6,7,8-hexahydro-4-phenylquinazolin-2(1*H*)-thiaone, considering advantages of cerric ammonium nitrate CAN as catalyst. We have used ethanol as solvent in this method. Our studies here in reports an efficient and facile method for the synthesis of 8-benzylidene-3,4,5,6,7,8-hexahydro-4-phenylquinazolin-2(1*H*)-thiaone.

2. Results and Discussion

We carried out synthesis of 8-benzylidene-3,4,5,6,7,8-hexahydro-4-phenylquinazolin-2(1*H*)-thiaone from the model reaction between of cyclohexanone 1, thiourea 2 and benzaldehyde 3. We examined effect of the different solvents and studied effect of the different catalysts and amount of

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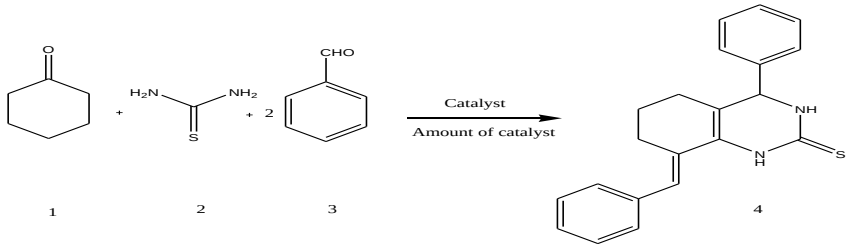
the catalysts on the reaction

Initially, when the catalytic amount was 10 mol % of the catalysts $AlCl_3$ and $FeCl_3$ were used both the catalysts were found to be unlucky to catalyze the reaction as the product yield were low after 10 hour stirring. When 10 mol % of the catalyst *L*-proline was used, low yield was obtained (Table 1, entry 3), but when catalyst CAN used in the reaction, yield was increased compared to all the three catalysts (Table 4, entry 1). Out of the these four catalysts were used, the catalyst CAN found to best as given high yield in low reaction time as compared to other catalyst used in the reaction. To examine the effect of amount of catalyst on the reaction, we decreased catalyst amount to 5 mol % but there was adverse effect as yield was lowered 41 %. When, 8 mol % catalyst amount used in the reaction there was lowered yield to 43 % was obtained.



(**Scheme 1)**.

Table 1 Optimization of the catalysts and the amount of the catalyst.

Entry	Catalyst	Mol %	Time (hr)	Yield[a] (%)
1	$AlCl_3$	10	10.00	41
2	$FeCl_3$	10	10.00	44
3	L-proline	10	7.00	39
4	CAN	10	4.30	69
5	CAN	05	5.00	41
6	CAN	08	5.00	43

[a] Isolated yield.

We further studied effect of different solvents on the reaction. In polar solvent such as methanol and water reaction showed poor performance but when ethanol was used as solvent, gives high yield and found best solvent for reaction. In case of non polar solvents such as toluene, Chloroform performance observed was more disappointing. Toluene as solvent gives only 29 % product after refluxing for 15 hours whereas in chloroform used as solvent, reaction was worked up after 12 hours and observed product was only 28 %.

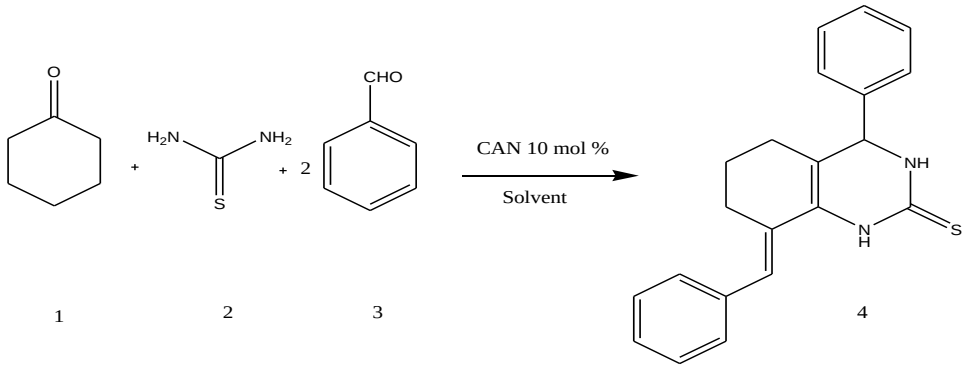


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Table 2. Optimization of the solvent.

Entry	Solvent	Catalysts	Mol %	Time (min)	Yield[a](%)
1	Methanol	CAN	10	7.00	42
2	Ethanol	CAN	10	4.30	69
3	Water	CAN	10	6.30	45
4	Chloroform	CAN	10	12.00	28
5	Toluene	CAN	10	15.00	29

[a] Isolated yield

With the optimized conditions in hand, we further examined the scope and the limitation of the reaction by using cyclohexanone with different aromatic aldehydes and thiourea or urea and the results are summarized in Table 3. When we taken benzaldehydes containing electron with drawing group substituent showed lower yield compared to the benzaldehydes containing the electron donating group. Benzaldehydes with donating group gives high yield this was because increased reactivity of the benzaldehydes. Highest yield were obtained when electron donating group such as methoxy present on the benzaldehyde along with the thiourea. When the urea was replaced by thiourea the product obtained in slightly higher percentage, this may be due to higher reactivity of the thiourea.

3. Experimental

General details

All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 x 20cm, Silica gel 60 F-254, Merck grade was used for thin layer chromatography to determine the progress of reaction. ^{1}H Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 300 MHz spectrometer. Melting points were measured in open capillary.

General procedure for synthesis of Quinazolin-2(1*H*)-thiaone or one derivative

To a mixture of aryl aldehyde 1 (2 mmol), cyclohexanone 2 (1 mmol), and urea or thiourea 3 (1.3 mmol) was added 10 mol% of ceric ammonium nitrate. The reaction mixture was reflux for 3-5 h. After the completion of the reaction (monitored by TLC analysis), the crude product was obtained by evaporation of solvent under reduced pressure. The solid thus obtained was further purified by re-crystallization using ethanol.

Product 4a:

Pale yellow solid, melting point 236-239 ^{o}C, **^{1}H NMR (300 MHz, DMSO)** d ¼ 1.96-2.04 (m, 1H), 2.49 (m, 1H), 2.69-2.79 (m, 2H), 5.15 (s, 1H), 6.53 (s, 1H), 7.11-7.28 (m, 11H), 8.88 (s, 1H).

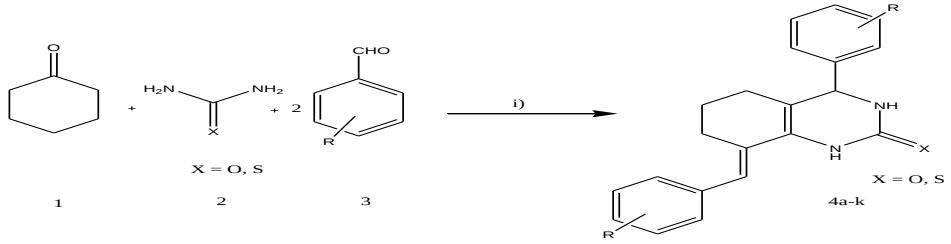

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Table 3. Synthesis various Quinazolin-2-(1*H*)-one/thione Derivatives.

Entry	R	X	Product	Reaction time. (hrs)	M.P. (^oC)	Yield (%)[a]
1	H	O	4-a	4.45	145	67
2	4-Cl	O	4-b	4.30	134	70
3	3-NO_2	O	4-c	4.45	230	60
4	4-NO_2	O	4-d	5.00	189	61
5	3-OCH_3, 4-OH	O	4-e	3.30	142	89
6	**H**	S	4-f	4.30	158	69
7	**4-Cl**	S	4-g	4.20	162	72
8	**3-NO_2**	S	4-h	4.30	178	63
9	**4-NO_2**	S	4-i	4.30	194	69
10	**3-OCH_3, 4-OH**	S	4-j	3.00	189	90
11	**3,4,5-OCH_3**	S	4-k	3.00	158	92

[a]isolated yield.

3. Conclusion

In conclusion, the present one-pot procedure provides an efficient and facile synthesis of heterobicyclic quanazolin-2-(1*H*) thiaone or one by CAN catalyzed condensation of aldehyde, cyclohexanone, and urea or thiourea in ethanol solvent under reflux conditions. We believe our procedure will find important applications in the synthesis of biologically active scaffolds to cater the needs of academia as well as pharmaceutical industries. Further exploration of this chemistry and biological evaluation of the synthesized scaffolds are in progress and will be reported in due course.

5.Acknowledgements

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