An Effective Synthesis of some Pyrimidinone derivatives by using CCl_3COOH as Catalyst under solvent free conditions

[1] Satheesh Ampolu author,[2]Nagesh L. Myadam,[3]Usha Hanumanthu [4]Manohar G. Chaskar, [5]Paul Douglas Sanasi

[1]Dept of Chemistry,
[1] Maha Raja's Degree College, Fort-Vizianagaram, India

Abstract : An eco–friendly and efficient method have been employed for the synthesis of hexahydroquinazolinone derivatives by the cyclization of Aromatic aldehyde, urea with cyclohexanone in the presence of trichloroacetic acid under solvent-free conditions. All the synthesized products have been characterized by FT-IR, 1H-NMR and MASS spectra.

IndexTerms **- Hexahydroquinazolinone derivatives, FT-IR, 1H-NMR and MASS, One pot synthesis, CCl_3COOH, Biginelli reaction..**

I. INTRODUCTION

Multi component reactions(MCRs) are important way for assembling two or more reactants and converting them into higher molecular weight compounds.The creation of C-C bond in organic molecules is been difficult and over the past few decades researcher have been showed interest on this area. Generally, heterogeneous catalysis is considerable over homogeneous catalysis due toit's dual applicability in fundamental research as well as industrial applications[1-4].

Biginelli reaction is one of the important carbon-carbon bond forming reaction in organic synthesis for the preparation pyrimidinone and its derivatives[5]-[7]. These constitutes an important natural and synthetic molecules, which havingimportantmedicinal and biological properties [8], [9]. The fused pyrimidinone with an arylidene group are important and essential heterocyclic motifs in anti viral, cyto-toxic [10], anti cancer properties [11], antitumor agents [12]. The classic version of the Biginelli reaction has been widely used in the preparation of collections of molecules in combinatorial synthesis [13],[14]. The newly method for the preparation of arylidene heterobicyclic pyrimidinones is the condensation reaction of aldehydes, urea and cyclohexanone named as Biginelli-type reactions. These reactions were carried out by using different catalysts i.e.Trimethylsilyl chloride (TMSCl) [15], ytterbium chloride [16], Tetrabutylammonium Hexatungstate ([TBA]2[W6O19]) [17], N-(4-sulfonic acid)butyl triethylammonium hydrogen sulfate ([TEBSA][HSO4]) [18], Phenylboronicacid [19], Lithium bromide (LiBr) [20], Zirconium chloride (ZrCl4) [21], Metal triflimide [22].

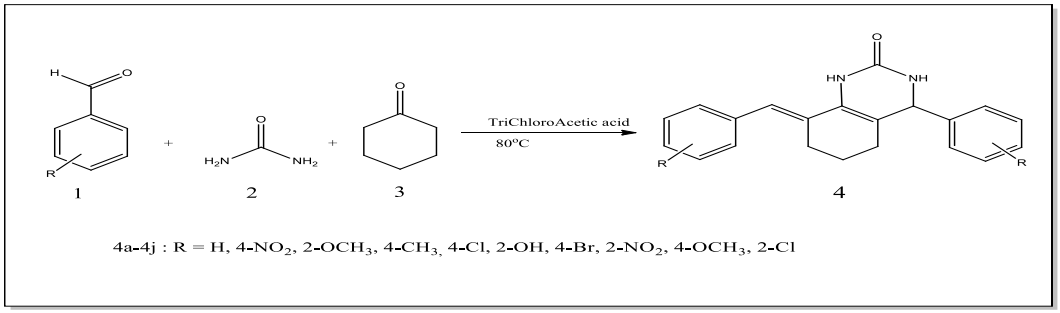
However, these methods suffer from some drawbacks such as long reaction time[15], lower yields[16], difficulty in product isolation [17], excess use of catalyst[18]. In view of environmental and economical aspects, there is an ongoing effort to replace the conventional catalysts by solid heterogeneous catalysts, this is mainly due to some advantages such as non toxicity, non corrosiveness, less expensive. The development of efficient and eco-friendly synthetic methodologies for the rapid construction of potentially bioactive compounds became a major task for chemists in organic synthesis. Improving the effectiveness of these MCRs with other strategies such as improving yield, short reaction time is the key component in the proposed method. The use of CCl_3COOH offer several advantages including higher yields, shorter reaction time .

Hence in continuation of our work to develop eco-friendly technique for heterocyclic synthesis an attempt has been made to synthesize hexahydroquinazolinone via Bizinelli reaction by the cyclization of aromatic aldehyde, urea and cyclohexanone in presence of CCl_3COOHas catalyst**(Scheme-1).**

II. EXPERIMENTAL

One pot synthesis of hexahydroquinazolinone derivatives

Aromatic Aromatic aldehyde(10mmol.), urea (10 mmol.) and Cyclohexanone(10 mmol.) and trichloro aceticacid (1 gm) were taken in a 50 ml round bottomed flask and was stirred . Then the reaction mixture was refluxed at 80oC for 10 minutes. The progress of the reaction was monitored by thin layer chromatography(n-Hexane, Ethyl acetate 4:1). After completion of the reactiona solid was obtained. It was washed with water and purified byre-crystalization from ethanol to get pure products. The corresponding products were confirmed by FT-IR, 1H-NMR, MASS spectral analysis**.(Table 1)**



Scheme1. Synthesis of hexahydroquinazolinone derivatives

3. Result and discussion

III. RESULT AND DISCUSSION

3.1 Comparative catalytic activity of $CCl_3COOH$with other catalysts for the synthesis of hexahydroquinazolinone. Reaction times for the formation of hexahydroquinazolinone with various catalysts are presented in Table 2. It is observed that with other catalysts and particularly under reflux conditions the reaction times are very much higher. Under reflux conditions, synthesis of hexahydroquinazolinone catalyzed by N-(4-sulfonic acid)butyl triethylammonium hydrogen sulfate ([TEBSA][HSO4]) [17], have been reported shorter reaction times, the present method offers a comparatively very low cost and easily producible CCl_3COOH for effective results.

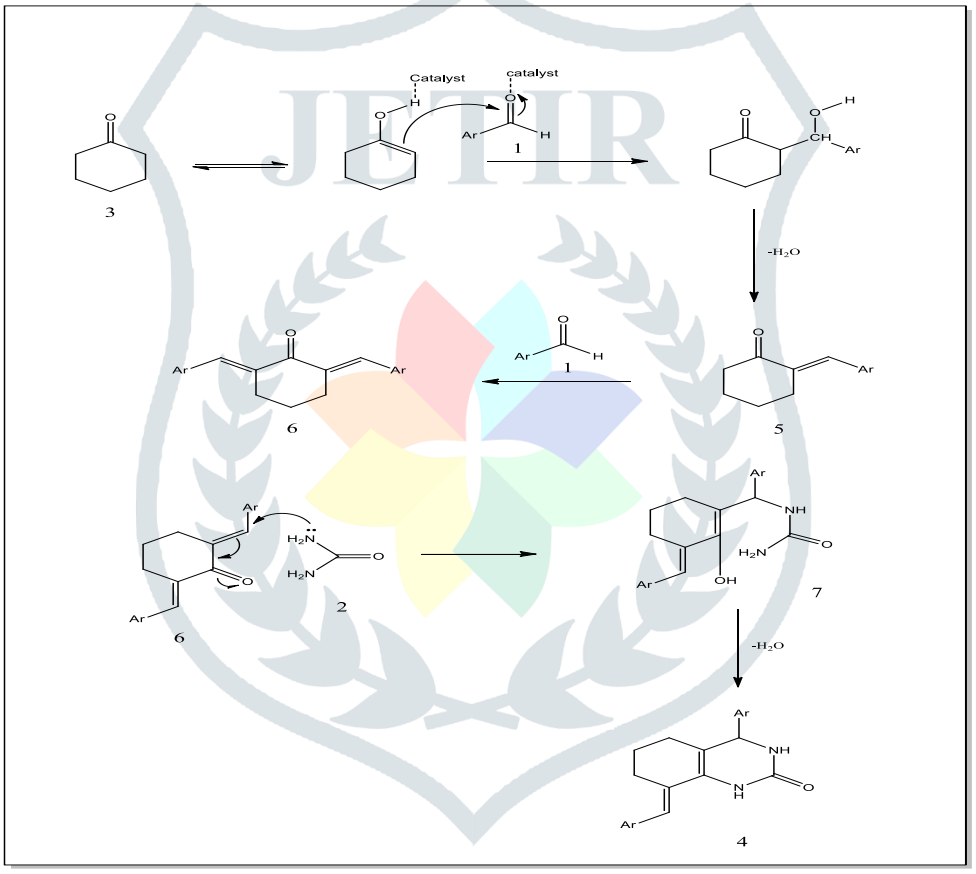
3.2 Effect of Temperature on Synthesis ofhexahydroquinazolinone

The reaction temperature for the formation of hexahydroquinazolin-2(1H)-one/thiones with nano copperferrite catalyst is 80°C is presented in table 3. It is observed that at below 80°C temperature yield of the product is low and reaction time is high. So we have confirmed 80°C is suitable temperature for this reaction.

3.3 Plausible mechanism for the formation of hexahydroquinazolin-2(1H)-one/thiones

It can be understood from the similar studies reported in the literature,[20] the suggested mechanism trichloro acetic acid catalyzed transformations is shown in scheme 2. As reported in the literature the Knoevenagel type coupling of benzaldehyde with cyclohexanone gives benzylidine 5. Further reaction of benzylidene 5 with benzaldehyde to provide α,α-bis(benzylidene cyclohexanone 6. Then compound 6 undergoes intramolecular cyclization to form the intermediate 7. From intermediate 7, a water molecule is eliminated to from the product hexahydroquinazolinone(Scheme 2).

Scheme-2 Plausible mechanism for the formation of hexahydroquinazolinone.



3.4 Spectral data for the synthesized hexahydroquinazolinone

8-benzylidene-4-phenyl-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(a)

Whit solid, IR(KBr) : 3444,3315(N-H str), 1664,1606(C=O Str), 1541,1450(Aromatic ,C=C Str), 1H NMR (400 mHz, CDCl3): δ 1.28-1.82(m,2H,CH2), 3.92-3.96(m, 4H, CH2), 7.02-7.04(m, 2H, CH), 7.39(s, 1H, NH-3), 7.41-7.77(m,10H, Ar-H), 9.93(s,1H,NH-1), ESI-MS m/z(%) :319 ([M+H]+ 100).

8-(4-nitrobenzylidene)-4-(4-nitrophenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(b)

Whit solid, IR(KBr) : 3479,3325(N-H str), 1657,1602(C=O Str), 1516, (Aromatic ,C=C Str), 1347(-NO2 Str),1H NMR (400 mHz, CDCl3): δ 1.58(m,2H,CH2), 3.92 (m, 4H, CH2), 7.02-7.04(m, 2H, CH), 7.53(s, 1H, NH-3), 7.70-7.88(m,10H, Ar-H), 9.91(s,1H,NH-1),ESI-MS m/z(%) :409 ([M+H]+ 100).

8-(2-methoxybenzylidene)-4-(2-methoxyphenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(c)

Whit solid, IR(KBr) : 3491,3316(N-H str), 1654,1596(C=O Str), 1516,1492(Aromatic ,C=C Str), 1042,1023¬(-OCH3),1H NMR (400 mHz, CDCl3): δ 3.82 (m,3H,-OCH3), 3.87-3.91(m, 6H, CH2), 7.02 (m, 2H, CH), 6.79(s, 1H, NH-3), 7.28-7.87(m,10H, Ar-H), 9.91(s,1H,NH-1),ESI-MS m/z(%) :379 ([M+H]+ 100).

8-(4-methylbenzylidene)-4-(p-tolyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(d)

Whit solid, IR(KBr) : 3437,3289(N-H str), 1678(C=O Str), 1587,1433(Aromatic ,C=C Str),1H NMR (400 mHz, CDCl3): δ 2.45(s,3H,CH3), 3.92 (m, 6H, CH2), 7.28-7.29(m, 2H, CH), 7.27(s, 1H, NH-3), 8.00-8.02(m,10H, Ar-H), 9.93(s,1H,NH-1),ESI-MS m/z(%) :346 ([M+H]+ 100).

8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(e)

Whit solid, IR(KBr) : 3448,3305(N-H str), 1662(C=O Str), 1597,1538(Aromatic ,C=C Str),754,718(-Cl Str),1H NMR (400 mHz, CDCl3): δ 1.58-2.60(m,2H,CH2), 3.92-3.96(m, 4H, CH2), 7.02-7.04(m, 2H, CH), 7.28(s, 1H, NH-3), 7.53-7.88(m,10H, Ar-H), 9.91(s,1H,NH-1),ESI-MS m/z(%) :388([M+H]+ 100).

8-(2-hydroxybenzylidene)-4-(2-hydroxyphenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(f)

Whit solid, IR(KBr) : 3327(N-H str),3232(-OH Str), 1688,1608(C=O Str), 1584,1504(Aromatic ,C=C Str), 1H NMR (400 mHz, CDCl3): δ 1.28-2.15(m,2H,CH2), 3.91-3.99(m, 4H, CH2), 4.15(m,1H, -OH) , 5.96(s, 1H, NH-3), 6.81-7.28(m,10H, Ar-H),ESI-MS m/z(%) :351 ([M+H]+ 100).

8-(4-bromobenzylidene)-4-(4-bromophenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(g)

IR(KBr) : 3443, 3308 (N-H str), 1659, 1603 (C=O Str), 1538, 1485 (Aromatic , C=C Str), 694, 589 (-Br Str); 1H NMR (400 mHz, CDCl3): δ 1.61-1.70 (m, 2H, CH2), 3.91-3.96 (m, 4H, CH2), 7.02-7.04 (m, 2H, CH), 7.23 (s, 1H, NH-3), 7.47-7.87 (m, 10H, Ar-H), 9.91(s, 1H, NH-1); ESI-MS m/z(%) : 477 ([M+H]+ 100).

8-(2-nitrobenzylidene)-4-(2-nitrophenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(h)

IR(KBr) : 3478, 3361(N-H str), 1673 (C=O Str), 1594, 1516(Aromatic , C=C Str), 1372, 1341 (-NO2 Str); 1H NMR (400 mHz, CDCl3): δ 1.62 (m, 2H, CH2), 7.28 (s, 1H, NH-3), 7.78-7.84 (m, 2H, CH), 7.97-8.15 (m, 10H, Ar-H), 10.45 (s, 1H, NH-1); ESI-MS m/z(%) :409 ([M+H]+ 100).

8-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(i)

IR(KBr) : 3441, 3334 (N-H str), 1667, 1602 (C=O Str), 1542, 1510 (Aromatic , C=C Str), 1028 (-OCH3 Str); 1H NMR (400 mHz, CDCl3): δ 1.62-1.71 (m, 2H, CH2), 2.36-3.95 (m, 4H, CH2), 4.09 (m, 3H, -OCH3) 7.02-7.09 (m, 2H, CH), 7.28 (s, 1H, NH-3), 7.85-7.87 (m, 10H, Ar-H), 9.91(s, 1H, NH-1); ESI-MS m/z(%) :379 ([M+H]+ 100).

8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(j)

IR(KBr) : 3433, 3308 (N-H str), 1664, 1606 (C=O Str), 1526, 1440 (Aromatic , C=C Str), 752, 724 (-Cl Str); 1H NMR (400 mHz, CDCl3): δ 1.74-1.90 (m, 2H, CH2), 2.34-3.96 (m, 4H, CH2), 7.02-7.04 (m, 2H, CH), 7.28 (s, 1H, NH-3), 7.34-7.98 (m, 10H, Ar-H), 8.00 (s, 1H, NH-1); ESI-MS m/z(%) :387 ([M+H]+ 100).

Table 1. Synthesis of hexahydroquinazolinone

S.No.	product	R	Time(min)	Yield(%)
1	4(a)	H	10	96
2	4(b)	4-NO_2	10	96
3	4(c)	2-OCH_3	12	95
4	4(d)	4-CH_3	11	96
5	4(e).	4-Cl	11	96
6	4(f)	2-OH	12	95
7	4(g)	4-Br	10	96
8	4(h)	2-NO_2	12	95
9	4(i)	4-OCH_3	11	96
10	4(j)	2-Cl	11	96

Table 2. Comparison of effect of the present catalyst with other catalysts on synthesis of hexahydroquinazolinone.

S.No.	Catalyst	Time(min)	Temperature(°C)	Yield(%)	Ref.
1.	ytterbium chloride	180	90	79	15
2.	[TEBSA][HSO_4]	10	100	88	17
3.	TMSCl	240	80	96	18
4.	$[TBA]_2[W_6O_{19}]$	60	80	91	19
5.	CCl_3COOH	10	80	96	Presentwork

Table 3. Effect of Temparature on the formation of hexahydroquinazolinone

S.No.	Catalyst	Temperature (ºC)	Time (min)	Yield (%)
1	CCl_3COOH	R.T.	180	20
2	CCl_3COOH	45	120	50
3	CCl_3COOH	65	45	75
4	CCl_3COOH	80	10	96

IV **CONCLUSION**

Trichloro acetic acid has been successfully used as catalyst for Biginelli reaction using aromatic aldehydes, cyclohexanone and urea. Utilization of this catalyst has several advantages: high yield, low catalyst loading, simplicity of performance, no formation

by-products, solvent-free condition, it follows along the line of green chemistry.The catalyst is readily available and inexpensive and can conveniently be handled and removed from the reaction mixture by washing with water.

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