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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2014, Vol. 30, No. (2):
Pg. 761-768

Cobalt(II) Chloride Catalyzed one Pot Synthesis of 2-substituted and 3-substituted-4(3H)-Quinazolinones

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http://dx.doi.org/10.13005/ojc/300249

(Received: February 15, 2014; Accepted: March 25, 2014)

ABSTRACT

Cobalt(II) chloride (10mol%) was found to be an efficient catalyst for one pot synthesis of variety of 2-substituted-4(3H)quinazolinones by condensation of anthranilamide and aldehydes and synthesis of 3-substituted-4(3H)quinazolinones by condensation of anthranilic acid, orthoester, primary amines at reflux giving good to excellent yields (75-95%).

Key words: Cobalt(II) chloride, 2-substituted and 3-substituted 4(3H)quinazolinones, Anthranilamide, aldehydes, anthranilic acid, $HC(OEt)_3$, anilines.

INTRODUCTION

The quinazolinone core and its derivatives form an important class of compounds, as they are present in a large family of products with broad biological activities. 4(3H)-quinazolinones are versatile nitrogen heterocyclic compounds, displaying a broad spectrum of biological and pharmacological activities such as anti-fungal,[1] anti-tumour,[2] hypotensive,[3]anti-cancer,[4,5]anti-HIV,[6]anti-inflammatory,[7]anti-bacterial,[8] etc. Furthermore, 4(3H)-quinazolinones substituted at 2,3-position derivatives play a pivotal role in the hypertensive activity.[9,10]

Several bioactive natural products such as febrifugine and isofebrifugine contain quinazolinone moieties with potential anti-malarial activity[11] Similarly quinazolinone containing moieties have been known as tyrosine kinase inhibitors,[12] dihydrofolate reductase inhibitors,[13] and tubulin polymerization inhibitors.[14] Due to their wide range of applications these compounds have received a great deal of attention in connection with their synthesis.

Many reagents have been reported in the literature,[15-26] for the synthesis of 4(3H)-quinazolinone derivatives. Among these methods 2-substituted-4(3H)quinazolinones have been

synthesized from anthranilamide and aldehydes using $NaHSO_3$,[16a] DDQ,[16b] $CuCl_2$,[20] $FeCl_3.6H_2O$,[25a] $Cu(NO_3)_2.3H_2O$,[25b] and 3-substituted-4(3H) quinazolinones were recently prepared by using various catalysts such as $Yb(OTf)_3$,[15h] Silicagel/ $FeCl_3$,[17a] Nafion-H,[17b] (a perfluorinated resin supported sulfonic acid), under microwave irradiation, $Zn(ClO_4)_2$,[18] heteropolyacids such as $H_3PW_{12}O_{40}.13H_2O$,[19] $La(NO_3)_3.6H_2O$,[21] $Bi(TFA)_3$-$FeCl_4$.[22]

In continuation of our work to develop new organic transformations,[27-29] we report here in that cobalt(II) chloride which acts as a mild lewis acid might be useful and inexpensive catalyst for the synthesis of 2-substituted-4(3H)quinazolinones and 3-substituted-4(3H)quinazolinones. Although cobalt(II) chloride has been extensively used as a mild catalyst for a variety of organic transformations,[30-32] there are no examples of the use of cobalt chloride as catalyst for the synthesis of 2-substituted-4(3H)-quinazolinones and 3-substituted-4(3H)quinazolinones.

In the present study 2-substituted-4(3H)quinazolinones and 3-substituted-4(3H) quinazolinones are synthesized and the results are presented here. A high yield condensation of anthranilamide, aldehyde (alkyl, aryl, heteroaryl) acetonitrile at reflux in the presence of catalytic amount of co(II) chloride, 2-substituted-4(3H)quinazolinones are obtained(scheme-1). 3-substituted-4(3H)quinazolinones are obtained from the reaction of anthranilic acid, triethyl ortho-formate ($HC(OEt)_3$) and anilines at reflux in the presence of catalytic amount of co(II) chloride, and acetonitrile as solvent(scheme-2).

MATERIAL AND METHODS

Chemicals were purchased from Merck and Fluka and directly used for the synthesis. Thin layer chromatography (TLC): precoated silica gel plates (60 F254, 0.2mm layer; E. Merck). ^{1}H NMR (Avance 300 MHz) spectra were recorded in DMSO using TMS as internal standard. Chemical shifts (´) are reported in ppm, Melting points (M.P.) were determined on a Fischer-Johns melting point apparatus. IR and MS were recorded on a Thermo Nicolet Nexus 670 FT-IR Spectrometer and Finnegan MAT 1020 Mass spectrometer operating at 70 ev. Elemental analyses were performed on a Perkin Elmer 2400series II Elemental CHN analyzer.

General procedure for the synthesis of 2-substituted-4(3H)quinazolinones

To a mixture of anthranilamide (1mmol) in acetonitrile (5mL), $CoCl_2$ (10mol%) was added to the appropriate aldehyde (1.3mmol) was refluxed at 70°C for the time specified in (Table-3) for each substrate, after completion of the reaction as indicated by TLC the reaction mixture was allowed to cool and quenched with $NaHCO_3$ followed by brine solution and extracted with ethyl acetate dried over Na_2SO_4, concentrated under vacuum, and the crude mixture was purified by column chromatography (hexane:ethylacetate 7:3) to afford the corresponding pure 2-substituted-4(3H)quinazolinones 3a-3m (Table-3). All the products are well characterized by spectral analysis (IR,^{1}HNMR, MS) and were found to be identical those reported in the literature.[20, 25]

General procedure for the synthesis of 3-substituted-4(3H)quinazolinones

To a mixture of anthranilic acid (1mmol) in acetonitrile (5mL) triethyl orthoformate ($HC(OEt)_3$) 1.5mmol), the appropriate aniline (1.3mmol) and $CoCl_2$ (10mol%) was refluxed at 70 °C for the time specified in (Table-4) for each substrate, after completion of the reaction as indicated by TLC the reaction mixture was allowed to cool and quenched with $NaHCO_3$ followed by brine solution and extracted with ethyl acetate dried over Na_2SO_4, concentrated under vacuum, and the crude mixture was purified by column chromatography (hexane:ethylacetate 7:3) to afford the corresponding pure 3-subtituted-4(3H) quinazolinones 7a-7o (Table-4). All the products are well characterized by spectral analysis (IR,^{1}HNMR, MS) and were found to be identical with those reported in the literature.[14b, 17-19, 21, 26]

Spectral data for selected compounds: 2-Phenyl-4(3*H*)-quinazolinone (3a)

mp (°C)[25] 237-239, IR(KBr): 679, 1458, 180, 1356, 1037, 965,738 cm^{-1}; ^{1}HNMR(300MHz, DMSO-d_6) 7.56-7.62 (m, 4H),7.75-7.84 (m, 2H), 8.18-8.53 (m, 3H),12.46 (s,1H, NH) ppm; Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.68; H, 4.51; N, 12.68; O, 7.5. Found:

C, 75.67; H, 4.48; N, 12.50. MS(EI): m/z (%) 222(M^+).

2-(4-Hydroxyphenyl-3-methoxy)-4(3*H*)-quinazolinone (3c)

mp(°C)[25]267-268, IR(KBr) 1664, 1578, 1545, 1483, 1280, 1248, 1027, 1025, 866, 770 cm^{-1}; ^{1}HNMR (300MHz, DMSO-d_6) 3.94 (s, 3H, CH_3), 6.98 (d, 1H, J=8:3Hz, Ph), 7.44 (t, 1H,J=7:4Hz, Ph), 7.75 (d, 1H, J=8:0Hz, Ph), 7.77 (d, 1H, J=8:3Hz,Ph), 7.80 (s, 1H, Ph), 7.86 (t, 1H, J=7:2Hz, Ph), 8.17 (d, 1H, J=7:8Hz, Ph), 9.85 (s, 1H, OH); 12.38(s, 1H, NH) ppm; Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.20; H, 4.53; N, 10.49. Found: C, 67.29; H, 4.60; N,10.30; MS (EI): m/z(%) 268.(M^+)

2-(4-Nitrophenyl)-4(3*H*)-quinazolinone (3i)

mp(°C)[25]>300, IR(KBr): 1682, 1609, 1590, 1523, 1469, 1348, 1151, 949 , 865, 772, 707, 556 cm^{-1}; ^{1}HNMR (300MHz, DMSO-d_6) 7.59 (t, 1H, J=7:5Hz, Ph), 7.80 (d, 1H, J=8:0Hz, Ph), 7.89 (t, 1H,J=7:6Hz, Ph), 8.19 (d, 1H, J=8:1Hz, Ph), 8.38 (d, 2H, J=9:1Hz, Ph), 8.43 (d, 2H, J=9:1Hz, Ph) 12.16(s, 1H, NH) ppm; Anal. Calcd for $C_{14}H_9N_3O_3$: C, 62.94; H, 3.40; N,15.72, Found: C, 62.79; H,3.56; N, 15.89; MS (EI): m/z(%) 267(M^+).

2-(Furyl)-4(3*H*)-quinazolinone (3f)

mp(°C)[25] 219–221, IR(KBr): 1663, 1618, 1569, 1457, 1330, 969, 775, 757cm^{-1}; ^{1}HNMR(300MHz, DMSO-d_6) 6.73(dd, 1H, J=3:4, 1.3Hz), 7.49 (t,1H, J=7:5Hz, Ph), 7.59 (d, 1H, J=3:4Hz), 7.68 (d, 1H, J=8:1Hz, Ph), 7.81 (t, 1H, J=7:6Hz, Ph), 7.97 (d, 1H, J=1:3Hz),8.11 (d, 1H, J=7:8Hz, Ph), 12.68 (s, 1H, NH) ppm; Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.98; H,3.76; N, 13.22. Found: C, 67.86; H, 3.79; N, 13.26; MS(EI): m/z (%) 212(M^+).

3-Phenyl-4(3*H*)-quinazolinone (7a)

mp(°C)[19] 139, IR (KBr): 1699, 1598, 1037, 1290, 1463,cm^{-1}; ^{1}HNMR(300MHz, DMSO-d_6): 8.34 (d, J =7.6 Hz, 1H), 8.16 (s, 1H), 7.72-7.78 (m, 2H), 7.51 (t, J=7.31 Hz, 1H) and 7.28-7.36 (m, 5H) ppm; Anal. Calcd. for $C_{14}H_{10}N_2O$:C,75.69; H,4.52; N, 12.65; O,7.2. Found: C,75.60; H,4.44; N,12.59; MS(EI): m/z (%) 222 (M^+).

3-(4-Bromophenyl)-4(3*H*)-quinazolinone (7c)

mp(°C)[19]186, IR(KBr):1692,1605, 1456, 1070cm^{-1}; ^{1}HNMR(300MHz, DMSO-d_6): 8.43(d, J = 8.6 Hz, 1H), 8.12 (s, 1H) and 7.95-7.21 (m, 7H) ppm; Anal. Calcd. for $C_{14}H_9BrN_2O$: C, 55.83; H, 3.09; Br, 26.55; N, 9.30. Found: C, 55.92; H, 3.07; N, 9.31; MS(EI): m/z(%), 300(M^+).

3-(4-Methylphenyl)-4(3*H*)-quinazolinone (7f)

mp(°C)[19] 148, IR(KBr): 1690, 1578, 1603, 1457cm^{-1}; ^{1}HNMR(300MHz,DMSO-d_6): 8.29 (d, J = 7.6 Hz, 1H), 8.11 (s, 1H), 7.69-7.71 (m, 2H),7.40(t, J= 7.2 Hz, 2H), 7.16 (d, J= 7.6 Hz, 2H), 7.28 (d, J= 7.6 Hz, 2H) and 2.26 (s, 3H)ppm; Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.17; N, 11.88; O, 6.97. Found: C, 76.29; H, 5.16; N, 11.77; MS(EI): m/z (%) 236 (M^+).

3-(2,5-Dichlorophenyl)-4(3*H*)-quinazolinone (7h)

mp(°C)[19] 146-148 IR(KBr):1673, 1604,1578 1450cm^{-1}; ^{1}HNMR(300MHz, DMSO-d_6): 8.43 (d, J= 7.6 Hz, 1H), 8.13 (s, 1H), 7.69-7.72 (m, 2H), 7.50 (t, J = 7.3 Hz, 1H), 7.38 (d, J= 7.6 Hz, 2H), 7.25 (d, J= 8.6 Hz, 2H)ppm; Anal.Calcd.for $C_{14}H_8Cl_2N_2O$: C,57.77; H, 2.79; Cl, 24.36; N,9.62. Found:C, 57.92; H,3.02; N, 9.35; MS(EI): m/z(%), 291(M^+).

3-(pyridin-2-yl)-4(3*H*)-quinazolinone (7i)

mp(°C)[18] 132-133 IR(KBr): 3061,1684, 1608,1474, 1435, 1328, 1290, 1256, 915, 870, 771 cm^{-1} ^{1}HNMR ((300MHz, DMSO-d_6); 8.65 (t, J= 7.3Hz, 2H), 8.40 (s,1H),7.90-7.92 (m, 2H), 7.78-7.84 (m, 2H), 7.54-7.57 (m, 1H), 7.39-7.41 (m,1H) ppm; Anal.Calcd for $C_{13}H_9N_3O$:C,69.97; H,4.08; N, 18.88. Found: C, 69.88; H, 3.99; N, 18.95; MS(EI): m/z(%), 223(M^+).

RESULTS AND DISCUSSION

In an effort to develop more widely applicable methodology, in order to optimize the reaction conditions initially we have studied the efficacy of cobalt(II) chloride by taking catalytic amount of 10 mol% and anthranilamide (1mmol) and benzaldehyde (1.3mmol) in acetonitrile (5mL) as model reaction(3a) refluxed at 70 °C for 5h, the reaction gave corresponding 2-Phenyl-4(3H)-quinazolinone 93% yield. (Table 3, entry 1). In the absence of cobalt(II) chloride even up to 15h no reaction was observed. The model reaction (3a) was performed in various solvents using cobalt(II) chloride as catalyst to identify the best medium for the reaction. A range of solvents such as $CHCl_3$,

DMF, THF, DCM, H_2O, DMSO, CCl_4, and CH_3CN were examined and acetonitrile emerged as the solvent of choice in terms of reaction kinetics and product yield (Table 1, entry 7). While comparing the effect of various catalysts on the model reaction (3a) we found that cobalt(II) chloride was more effective than other catalysts tested in terms of isolated yields (Table-2, (3a) entry 7). An optimum amount of 10mol% of cobalt(II) chloride is sufficient to carry forward the reaction.

Table 1: Screening of solvents for the synthesis of 2-phenyl-4(3H)quinazolinone (3a) from anthranilamide (1mmol) aldehyde (1.3mmol) and 3-phenyl-4(3H)quinazolinones (4a) from anthranilic acid (1mmol) aniline (1.3mmol) and triethyl-orthoformate (1.5mmol) heating at 70°C in the presence of cobalt (II) chloride (10mol%).

Entry	Solvent (5ml)	Time (hours)		Yield (%)	
		3a	4a	3a	4a
1	$CHCl_3$	9	8	40	45
2	DMF	9	8	50	56
3	THF	9	8	45	55
4	CCl_4	10	9	55	50
5	H_2O	12	12	50	48
6	DMSO	9	9	50	50
7	CH_3CN	5	6	93	95
8	No solvent	12	12	NR*	NR*

*NR: No Reaction

Table 2: Screening of various catalysts (10mol%)as standard for the synthesis of 2-phenyl-4(3H) quinazolinone (3a) from anthranilamide (1mmol) aldehyde (1.3mmol), acetonitrile (5mL) and 3-phenyl-4(3H)quinazolinones (4a) from anthranilic acid (1mmol), triethyl orthoformate (1.5mmol) aniline (1.5mmol), acetonitrile (5mL) and heating at 70 °C

Entry	Catalyst (10mol%)	Time (hours)		Yield (%)	
		3a	3a	4a	4a
1	$Al(NO_3)_3.3H_2O$	9	9	40	45
2	$Ni(NO_3)_3.3H_2O$	9	9	45	50
3	$Nd(NO_3)_3.3H_2O$	8	8	60	65
4	$Zn(NO_3)_2.3H_2O$	8	8	65	70
5	Cu-Proline	8	9	35	45
6	Zn-Proline	9	9	40	46
7	$CoCl_2$	5	6	93	95
8	TBABr	9	8	25	NR*
9	$K_4Fe(CN)_6$	9	9	35	35
10	$Rh(NO_3)_3.3H_2O$	9	8	45	60
11	$Ce(NH_4)_2.3H_2O$	9	9	60	55
12	$Na_2MoO_4.2H_2O$	9	9	NR*	25

* NR: No Reaction

Encouraged by the results obtained for benzaldehyde (3a) we generalized the reaction scope for a number of other structurally divergent aromatic aldehydes, aliphatic aldehydes such as (propanaldehyde, butyraldehyde, and acetaldehyde, Table 3, entry 1j, 1k, 1l) heterocyclic aldehydes (furan-2 aldehyde, thiophene-2 aldehyde Table 3, entry 1f, 1m). In general electron rich counter parts such as hydroxy, methoxy, methyl groups require less reaction time than those of electron withdrawing groups such as (nitro group, halide group) were employed and reacted well to give the corresponding 2-substituted 4(3H)quinazolinones.

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Table 3: Synthesis of 2-substituted -4(3H)quinazolinones by the reaction of aliphatic, aromatic and hetero aromatic aldehydes with anthranilamide, catalyzed by cobalt (II) chloride in acetonitrile at 70 °C

Entry	Aldehyde **(2)**	Product **(3a-3m)**[a]	Time (hours)[c]	Yield (%)[b]	mp(°C)/Reference	
1a	C_6H_5CHO	**3a**	5	93	237-239	25
1b	4-$OCH_3C_6H_4CHO$	**3b**	5	90	243-244	25
1c	4-OH-3-$OCH_3C_6H_3CHO$	**3c**	5	84	267-268	25
1d	4-OHC_6H_4CHO	**3d**	5	80	>300	25
1e	4-$N(CH_3)_2C_6H_4CHO$	**3e**	6	83	240-241	25
1f	C_4H_3OCHO	**3f**	7	78	219-222	25
1g	4-ClC_6H_4CHO	**3g**	7.5	75	>300	25
1h	4-BrC_6H_4CHO	**3h**	6	80	293-295	25
1i	4-$NO_2C_6H_4CHO$	**3i**	7	78	>300	25
1j	CH_3CH_2CHO	**3j**	7	84	230-232	25
1k	$CH_3CH_2CH_2CHO$	**3K**	7.5	83	200-203	25
1l	CH_3CHO	**3l**	7	82	240-242	25
1m	C_4H_3SCHO	**3m**	7.5	80	219-221	20

[a]All the products are characterized by spectral analysis [b] Isolated yields [c] heating at 70^0C

groups require less reaction time than those of electron withdrawing groups such as (nitro group, halide group) were employed and reacted well to give the corresponding 2-substituted 4(3H)quinazolinones.

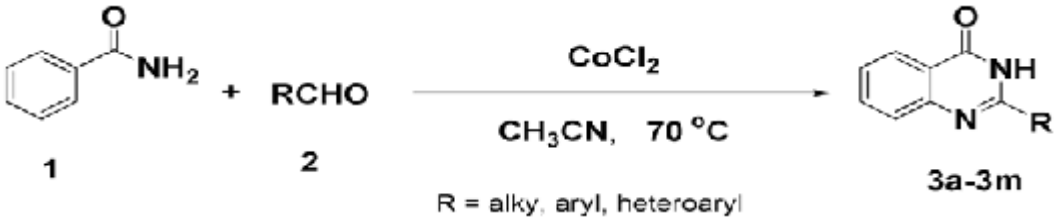
In view of the above results obtained for the synthesis of 2-substituted-4(3H) quinazolinones, we wish to explore the use of cobalt (II) chloride as catalyst for the synthesis of 3-substituted-4(3H)quinazolinone (scheme-2). The treatment of anthranilic acid, triethyl orthoformate ($CH(OEt)_3$), primary amines, in acetonitrile as solvent and cobalt(II) chloride (10mol%) as catalyst, heating at 70 °C for the time specified for each substrate in (Table-4) resulting in the formation of 3-substituted4(3H)quinazolinones.

In a similar fashion we studied the efficacy of different catalyst chosen (10mol%) as standard on the model reaction (4a) by taking anthranilic acid, triethyl orthoformate, aniline, acetonitrile, (5mL),

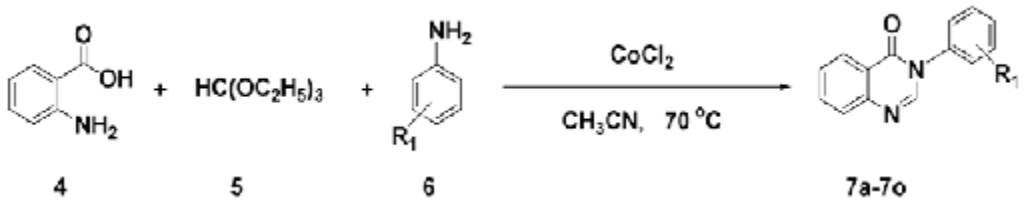
Table 4: Synthesis of 3-substituted 4(3H)quinazolinones by the reaction of anthranilic acid (4), $HC(OEt)_3$ (5), aromatic amines, catalyzed by cobalt (II) chloride in acetonitrile at 70°C.

Entry	$R\text{-}NH_2$ **(6)**	Product **(7a-7o)**[a]	Time (hours)[b]	Yield (%)[c]	mp(°C)	Reference
2a	$C_6H_5NH_2$	**7a**	6	95	139	19
2b	$2\text{-}ClC_6H_4NH_2$	**7b**	7	86	178	14b
2c	$4\text{-}BrC_6H_4NH_2$	**7c**	7	85	186	19
2d	$2,4\text{-}(CH_3)_2C_6H_3NH_2$	**7d**	7	82	Liquid	14b
2e	$4\text{-}OCH_3C_6H_4NH_2$	**7e**	6	80	195	19
2f	$4\text{-}CH_3C_6H_4NH_2$	**7f**	6	85	147	19
2g	$4\text{-}ClC_6H_4NH_2$	**7g**	7	82	192	14b
2h	$2,5\text{-}Cl_2C_6H_3NH_2$	**7h**	7	80	147	19
2i	$2,6\text{-}Cl_2C_6H_3NH_2$	**7i**	7.5	78	253	19
2j	$3\text{-}NO_2C_6H_4NH_2$	**7j**	7	78	200-202	14b
2k	$2\text{-}NH_2C_5H_4N$	**7k**	7	80	131-132	18
2l	$3\text{-}OCH_3C_6H_4NH_2$	**7l**	7	80	196	14b
2m	$4\text{-}NO_2C_6H_4NH_2$	**7m**	7	80	199-200	14b
2n	$3,4\text{-}Cl_2C_6H_3NH_2$	**7n**	7.5	75	164-168	19
2o	$2\ ,4\text{-}Cl_2C_6H_3NH_2$	**7o**	8	78	232-234	19

[a] All the products are characterized by spectral analysis [b] refluxed at 70 °C [c] isolated yields



Scheme 1: Synthesis of 2-substituted-4(3H)quinazolinones



Scheme 2: Synthesis of 3-substituted- 4(3H)quinazolinones

heating at 70 °C for 6 hours results in the formation of 3-phenyl-4(3H)quinazolinone in 95% yield (Table-2, (4a) entry 7). The results shown that cobalt(II) chloride is emerged as best catalyst both in terms of reaction time and yields. Model reaction (4a) is screened for the best solvent by taking various solvents and acetonitrile is emerged as the best solvent (Table-1 4a, entry 7). Various 3-substituted 4(3H)quinazolinone were prepared by using structurally varied anilines including pyridine-2-amine (Table-4 entry 2k). All the 2-substituted-4(3H)quinazolinones and 3-substituted-4(3H)quinazolinones are well characterized by spectral analysis and with authentic samples.

CONCLUSION

In conclusion we have developed clean and efficient alternative protocols for the synthesis of 2-substituted-4(3H)quinazolinones from anthranilamide, aldehydes and synthesis of 3-substituted-4(3H)quinazolinones from three component reaction of anthranilic acid, triethyl orthoformate, primary amines. The notable feature of these methodologies are by using a mild, inexpensive, easily available, cobalt (II) chloride as catalyst. We believe that this methodology will be a valuable addition for the synthesis of 2-substituted-4(3H)quinazolinones and 3-substituted-4(3H)quinazolinones which are important synthetic interest because of their pharmacological and therapeutic properties such as anti-inflammatory, antiviral, anticancer activities etc…..

ACKNOWLEDGEMENTS

Dr. Aayesha Nasreen thanks Jazan University, for giving her an opportunity to continue research.

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