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$COFE_2O_4$-NPS CATALYTIC ACTION IN THE SYNTHESIS OF 2-SUBSTITUTED 4(3*H*)-QUINOZOLINONES SUBSIDIARIES FROM ISATOIC ANHYDRIDE

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ABSTRACT
A profoundly productive synthesis of 2-substituted 4(3H)-quinazolinones is explained utilizing $CoFe_2O_4$-NPs catalyzed coupling of isatoic anhydride and benzamidine subordinates at room temperature. This reaction continues under mellow conditions. This technique was seen as better strategy giving high yields. The present technique gives a few advantages, for example, short response times and upgraded selectivity. The Structures of the Compounds are affirmed by ^{1}H NMR and ^{13}C NMR, Mass spectral information.

KEY WORDS: 2-substituted 4(3H)-quinazolinone, benzamidine, isatoic anhydride, Nano particle catalyst.

INTRODUCTION
Quinazolinones are combined heterocyclic aggravates that having a broad cluster of organic exercises. Quinazolinones are fused heterocyclic compounds that possessing an extensive array of biological activities. Quinoxalinone and its subsidiaries have increased a lot of consideration in the ongoing past as a significant pharmacore in the group of various naturally dynamic heterocyclic mixes. Its subsidiaries have been utilized as manufactured forerunners for some antihypertensive and pain relieving drugs[I-IX]. Besides, quinazolinone subordinates are related with a few significant natural exercises, for example, anti-cancer[X], anti-inflammation[XI], anti-bacterial[XII], anti-virus[XIII], anti-tuberculosis[XIV], anti-malarial [XV], anti-hypertensive [XVI], anti-obesity, anti-psychotic, anti-diabetes [XVII].
Quinazolinones represent a class of advantaged frameworks that happen in around 150 normally occuring alkaloids, some of which show a wide scope of organic and pharmacological activities, for example, rutaecarpine, luotonin A, luotonin F, sildenafil, bouchardatine and raltitrexed [XVIII]. Although various strategies have been developed [XIX] , the recently announced conditions required to impact the union incorporate metal catalysts, organic solvents or potentially explicit oxidants.
Various manufactured conventions have been produced for the preparation of 2-substituted 4(3*H*)-quinozolinones. The most traditional and general conventions for the union of quinazolinones are still through the buildup between o-aminobenzamides and aldehydes

pursued by the oxidation of the subsequent aminal intermediates [XX]. One of the most widely recognized methodologies is the cyclization of anthranilamides with aldehyde within the sight of different advancing agents, for example, $NaHSO_3$ [XXI], p-toluenesulfonic acids/DDQ[XXII], I_2 [XXIII], $CuCl_2$ (3.0 equiv) [XXIV], and $FeCl_3$ (2.0 equiv) [XXV]. The most widely recognized manufactured strategy included buildup of aryl-1,2-diamines with 1,2-dicarbonyl compounds [XXVI]. Other imperative combinations of quinoxaline and related compounds incorporate multicomponent reaction (MCR) [XXVII] and so on. Thriveni P., Hari Krishna M. *et al.,* reported the synthesis of substituted quinazolinone subsidiaries by one-pot reaction/Tandem cyclization from different beginning materials like isatoic anhydride, halobenzoic acids, Halobenzamide, anthranilic acid, amines and ortho esters utilizing BBr_3, Cerium(III) chloride, AgoTf as successful catalyst [XXVIII-XXXIII] in spite of these amazing endeavors, advancement of a efficient methodology for the union of profoundly functionalized 2-substituted 4(3*H*)- quinozolinones subsidiaries is as yet a significant test for organic scientific experts. in this we report *$CoFe_2O_4$-NPs* catalyzed basic and proficient strategy for the synthesis of 2-substituted quinazolinones from isatoic anhydride and aryl imidamides in high yield (**Scheme 1**).

EXPERIMENTAL SECTION

Melting points were determined in open-end capillaries and are uncorrected. Synthesized molecules were checked for the purity by TLC on silica gel G plates and spots were located by iodine vapors. ^{1}H NMR spectra were measured on BRUKER ADVANCE iI 400 NMR Spectrometer using TMS as internal standard. The mass spectra were observed and recorded on a JEOL 5x102/DA-6000 mass spectrometer. The iR spectra were measured on Perkin-Elmer spectrum RX iFT-IR System using KBr pellets. Essential examinations of the recently incorporated compounds were done on Perkin Elmer model 2400 C H N analyzer. Every one of the compounds gave acceptable essential investigation inside ±0.4% of hypothetical esteems. All responses were done under argon in broiler dried dish sets with attractive blending. Except if generally noticed, all materials were acquired from business providers and were utilized moving along without any more refinement. All solvents were reagent grade. THF was refined from sodium benzophenone ketyl and degassed altogether with dry argon straightforwardly before use.enzophenone ketyl and degassed thoroughly with dry argon directly before use. Except if generally noted, organic extracts were dried with anhydrous Na_2SO_4, sifted through a fritted glass funnel, and thought with a rotating evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by utilizing the versatile stage showed. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^{1}H for ^{13}C, respectively, in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-*d* or DMSO-*d*6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm, DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm.

(i) General procedure for preparation of cobalt ferrite nanoparticles (CoFe2O4-NPs):[XXXIV]

The solutions of iron nitrate $Fe(NO_3)_3.\ 9H_2O$ (0.2M, 10 mL) and cobalt nitrate $Co(NO_3)_2.6H_2O$ (0.1M, 10 mL) were arranged independently and combined. An solution of NaOH (3 M) was added gradually to the jar, until p^H to arrive at 12. At long last, oleic acid (3 drops) was added to the solution as surfactant. At that point, the suspension was

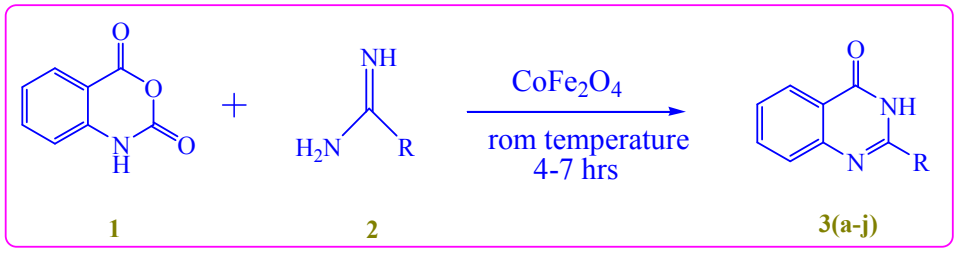
enthusiastically mixed utilizing a mechanical stirring at 90°C for 2 h. After complete precipitation, the residue was washed with double distilled water (3×25 mL). Finally, the mixture was isolated by magnetic bar and dried under vacuum oven at 50°C for overnight.

(ii) General Procedure for the Synthesis of isatoic anhydride: [XXXV]
In a round bottom flask, to a mixture of water (500 l.) and concentrated hydrochloric acid (63 ml), the beginning material Anthranilic acid (0.5 mole) was included with delicate warming. Subsequent to dissolving anthranilic acid in the solution, the solution is filtered and poured into round bottom flask with magnetic stirrer. With the stirrer in quick movement, phosgene is passed into the solution of anthranilic acid at 50°C and the flow of phosgene is proceeded for 2–4 hours or until the rate of absorption is clearly much decreased. isatoic anhydride appears as a precipitate. The product is gathered on a Buchner funnel and is washed with three 50 ml segments of cold water. The precipitated isatoic anhydride is gathered on a filter and washed. The product is dried in air and afterward at 100°C to get isatoic anhydride.

(iii) General Procedure for the Synthesis of 2-substituted 4(3*H*)-quinozolinones 3(a-j):
In a round-bottomed flask equipped with a condenser and a magnetic stirrer, isatoic anhydride (1 mmol) in 1,4-dioxane (12 vol) was added with benzimidamide (1.1 mmol) followed by cobalt ferrite nanoparticles (2 mg). The reaction mixture was mixed at room temperature for 4-7 hrs. The progress of the reaction was observed by TLC (eluent: n-hexane/ethyl acetate). After completion of the reaction CH_2Cl_2 (20 mL) was included and the catalyst was separated by centrifuge. The catalyst was washed and dried. The residue was purged through the silica gel chromatography chromatography utilizing ethyl acetate and hexane (30:70) as eluent to acquire the comparing items in 80-92 % yields.

Scheme I: The synthetic route was depicted in Scheme I

Scheme I



Synthesis of 2-Substituted Quinazolinone derivatives

Spectral data for selected compounds:

2-methylquinazolin-4(*3H*)-one (3a):
White solid, mp: 176-177°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.19 (s, 1H), 8.28 (dd, *J*1 =8.0 Hz, *J*2 = 1.2 Hz, 1H), 7.76 (dt, *J1* = 8.4 Hz, *J2* = 1.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.47 (dt, *J1* = 8.4 Hz, *J2* = 1.2 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.1, 120.2, 126.2, 126.4, 127.0, 134.9, 149.4, 153.3, 164.4.
2-phenylquinazolin-4(*3H*)-one (3b):
white solid, yield, mp 231–233 °C. ^{1}H NMR (DMSO-d6, 400 MHz): δ 7.49–7.59 (m, 4H), 7.73 (d, J = 8.4 Hz, 1H), 7.80–7.84 (m, 1H), 8.13–8.18 (m, 3H), 12.55 (s, 1H). ^{13}C NMR

(DMSO-d6, 100 MHz) d 121.4, 126.3, 127.1, 128.0, 128.2, 129.1, 131.9, 133.2, 135.1, 149.2, 152.8, 162.7.

2-ethylquinazolin-4(*3H*)-one (3c):

White solid, mp: 232-233°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.80 (s, 1H), 8.29 (d, *J* 7.6 Hz, 1H), 7.78 (dt, *J1* = 8.0 Hz, *J2* =1.2 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 2.84 (q, *J* = 7.6 Hz,2H), 1.46 (t, *J* = 7.6 Hz, 3H): ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.5, 29.2, 120.5, 126.2, 126.4, 127.2, 134.8, 149.4, 157.5,164.2.

2-isopropylquinazolin-4(*3H*)-one (3d):

White solid, mp: 232-233°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.95 (s,1H), 8.29 (d, *J* = 7.6Hz, 1H), 7.70-7.79 (m, 2H), 7.47 (t, *J* = 8.0 Hz, 1H), 2.97-3.08 (m, 1H), 1.44 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.5, 35.0, 120.8, 126.3, 126.4, 127.4, 134.7, 149.4, 160.5,163.7.

2-(4-oxopentyl)quinazolin-4(*3H*)-one (3e):

White solid, mp: 145-146°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.52 (s, 1H), 8.29 (dd, *J*1 = 8.0 Hz, *J*2 =1.2 Hz, 1H), 7.77 (dt, *J1* = 8.0 Hz, *J2* = 1.6 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.48 (dt, *J1* = 8.0 Hz, *J2* = 1.2 Hz, 1H), 2.18 (s, 3H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.13-2.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1, 30.0, 34.7, 42.3, 120.6, 126.3, 126.5, 127.2, 134.8, 149.2,155.8, 163.8, 208.2.

2-hexylquinazolin-4(3H)-one (3f):

White solid. Mp: 145 – 146°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.11 (s, 1H), 8.05 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.77 – 7.69 (m, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.38 (m, 1H), 2.61 – 2.51 (m, 2H), 1.75 – 1.63 (m, 2H), 1.27 (d, *J* = 15.2 Hz, 6H), 0.81 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.28, 157.97, 149.43, 134.69, 127.24, 126.32, 126.12, 121.24, 34.96, 31.38, 28.64, 27.19, 22.40, 14.34.

2-(p-tolyl)quinazolin-4(3H)-one (3g):

light yellow solid, mp 238–240 °C. ^{1}H NMR (DMSO-d6, 400MHz): δ 2.34 (s, 3H), 7.30 (d, J = 8.0 Hz, 2H), 7.45–7.49 (m, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.77–7.81 (m, 1H), 8.08 (d, J = 8.4 Hz, 2H), 8.13 (d, J = 7.2 Hz, 1H), 12.42 (s, 1H); ^{13}C NMR (DMSO-d6, 100 MHz): δ 21.4, 121.4, 126.3, 126.8, 127.9, 128.1, 129.6, 130.4, 134.9, 141.9, 149.4, 152.7, 162.7.

2-(4-chlorophenyl)quinazolin-4(3H)-one (3h):

White solid. Mp: 298 – 299°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.57 (s, 1H), 8.21 – 8.16 (m, 2H), 8.13 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.82 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.54 – 7.49 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.78, 151.96, 149.02, 136.74, 135.10, 132.13, 130.10, 129.15, 127.91, 127.21, 126.35, 121.47.

2-(4-fluorophenyl)quinazolin-4(3H)-one (3i):

White solid. Mp: 257 – 259°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.53 (s, 1H), 8.26 – 8.20 (m, 2H), 8.13 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.82 (dd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H),7.50 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 7.40 – 7.33 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.76, 162.97, 151.84, 149.13, 135.10, 130.84, 129.70, 127.93, 127.08, 126.32, 121.37, 116.09.

2-(4-methoxyphenyl)quinazolin-4(3H)-one* (*3j):

light yellow solid, mp 238–240 °C. ^{1}H NMR (DMSO-d6, 400 MHz): δ 3.82 (s, 3H), 7.06 (d, J = 8.8 Hz, 2H), 7.45 (t, J =8.0 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H), 8.17 (d, J = 8.4 Hz, 2H), 12.37 (s, 1H); ^{13}C NMR (DMSO-d6, 100 MHz): δ 55.9, 114.5, 121.2, 125.3, 126.3, 126.5, 127.8, 129.9, 134.9, 149.5, 152.3, 162.4, 162.7.

RESULTS AND DISCUSSION

A progression of 2-substituted Quinazolinone subsidiaries 3(a-j) incorporated from isatoic anhydride and benzimidamide utilizing cobalt ferrite nanoparticles. This technique was seen as better strategy giving high yields. A progression of aldehydes with either electron-giving or electron withdrawing groups attaching to aromatic ring were examined. The substitution groups on the aromatic ring had no undeniable impact on the yield.

CONCLUSION

All in all, we have built up a straightforward strategy for the preparation of 2-substituted Quinazolinone subsidiaries from isatoic anhydride and benzimidamide utilizing cobalt ferrite nanoparticles at room temperature. The response continues under gentle conditions with great to magnificent yields. in this manner, the created strategy could be an option for the scholarly just as modern applications.

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