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**Preparation of skeletally diverse quinazoline-2,4(1H,3H)-diones using Na$_2$SiO$_3$/SnFe$_2$O$_4$ catalytic system through a four-component reaction**

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**Abstract:** Sodium silicate with the formula of Na$_2$SiO$_3$ was used for the four-component reaction of ketones, aldehydes and cyanoacetamide. The effect of SnFe$_2$O$_4$ nano-particles on the catalytic potential of Na$_2$SiO$_3$ was investigated. The desired products synthesized by this method are 5-amino-7-aryl-2,4-dioxo-2,3,4,4a,7,7a,8,9,10,11-decahydro-1H-benzo[i]quinazoline-6-carbonitriles, 5-amino-2,4-dioxo-7-aryl-1,2,3,4,4a,7,7a,8,10,11-decahydroxy[3,4-i]quinoxaline-6-carbonitrile, 5-amino-9-methyl-2,4-dioxo-7-aryl-2,3,4,4a,7,7a,8,9,10,11-decahydro-1H-pyrido[3,4-i]quinazoline-6-carbonitrile and 5-amino-2,4-dioxo-7-aryl-1,2,3,4,4a,7,7a,8,10,11-decahydrothiopyrano[3,4-i]quinazoline-6-carbonitrile derivatives. This method has advantages of high yields, simple procedure and easy work-up.

**Keywords:** quinazoline-2,4(1H,3H)-diones; Na$_2$SiO$_3$; SnFe$_2$O$_4$ nano-particles; benzo[i]quinazoline; pyrano[3,4-i]quinazoline; thiopyrano[3,4-i]quinazoline

1 Introduction

Heterocycles bearing quinazoline core structures played a significant role in research fields such as chemistry, drug development and biological investigations (Ghashang, 2012; Ghashang et al., 2013, 2015). Quinazoline and especially quinazoline-2,4(1H,3H)-dione derivatives have attracted significant attention due to diverse pharmacological activities such as anti-proliferative activities against HCT-116 and MCF-7 cell lines (Hei et al., 2016), anti-proliferative activity in LNCaP and prostate cancer cell lines (Maestri et al., 2017), isoform-selective PI3K-α inhibition (Yadav et al., 2016), PARP-1/2 inhibition activity (Zhou et al., 2018).

Quinazoline-2,4(1H,3H)-dione moiety could be constructed by cyclization of 2-aminobenzonitrile with DMF (Rasal and Yadav, 2016), the reaction of CO$_2$ and 2-aminobenzenitriles (Ma et al., 2013), carbonylation and then cyclization of anthranilamide (Li, 2009), and treatment of substituted anthranilic acid with potassium cyanate (El-Brollosy, 2007). However, quinazoline-2,4(1H,3H)-diones can be synthesized via many methods but most of them suffer from structure diversity and scope expanding. A new method for the preparation of important scaffolds with a core of quinazoline-2,4(1H,3H)-dione has been developed by Jiang et al. through a multicomponent reaction of aldehydes, cycloketones, and cyanoacetamide under MW irradiation conditions using K$_2$CO$_3$ and Cs$_2$CO$_3$ as basic catalysts (Jiang et al., 2009, 2016).

Sodium silicate with a general formula of SiO$_2$(Na$_n$O)$_m$ is a white powder that dissolves easily in water and provides an alkaline solution which is stable in neutral and alkaline media. Depending on their prepared ways and purity, sodium silicate has a unique chemistry and has own industrial and consumer applications. One of the important uses of sodium silicate is its use in the manufacture of detergents and ceramic and tile industries. The participation of sodium silicate in the composition of detergents will control the corrosion and alkaline attack. It also acts as a melting aid and prevents cracking of biscuits (Ebnesajjad, 2011; Lagaly et al., 2005). The use of sodium silicate increased stiffness and reduced permeability in predominantly granular soils. Impregnation of concrete with sodium silicate reduces porosity and increases its longevity. Sodium silicates are known to reduce lead, copper and other heavy metals in...
drinking water and reduce the calcium and magnesium hardness (Ebnesajjad, 2011; Lagaly et al., 2005). Their function is used as a corrosion inhibitor to form a microscopic film on the inside of the water pipe and to prevent the formation of bells. Silicates are used to remove oil, wax, and soot from cotton in the weaving industry. In agriculture, soluble silicates are a vital nutrient for plant health and, in small quantities, increase plant resistance to disease and increase yields. The use of sodium silicate reduces the friction resistance to 5%, which results in less fuel consumption for trucks and trucks (Ebnesajjad, 2011; Lagaly et al., 2005).

Sodium silicate has been used for the acceleration of numerous organic transformations such as biodiesel production (Guo et al., 2010), production of lactic acid from rapeseed oil (Long et al., 2011), transesterification of soybean oil to biodiesel (Guo et al., 2012), transesterification of waste cooking oil to biodiesel (Daramola et al., 2015), preparation of Pyrano [2,3-d] pyrimidine derivatives (Abaszadeh et al., 2019), synthesis of pyrano[2,3-d] pyrimidines (Sheikhan-Shamsabadi and Ghashang, 2017), preparation of 2-amino-5-oxo-4-aryl-4,5-dihydroindeno[1,2-b] pyran-3-carbonitriles (Fazlinia and Sheikh, 2018), preparation of Pyrido[2,3-b] indoles (Sheikh and Fazlinia, 2018).

In this, we aim to investigate the effect of SnFe$_2$O$_4$ nano-particles on the catalytic activity of Na$_2$SiO$_3$ and to prepare a series of quinazoline-2,4(1H,3H)-dione through a multi-component reaction of aldehydes, cycloketones, and cyanoacetamide under solvent-free conditions using a mixture of SnFe$_2$O$_4$/Na$_2$SiO$_3$ (Scheme 1).

2 Results and discussion

X-ray diffraction patterns (XRD) of pure SnFe$_2$O$_4$ nanoparticles and sodium silicate combined with different ratios of SnFe$_2$O$_4$ nanoparticles are shown in Figure 1. Accordingly, SnFe$_2$O$_4$ nanoparticles have amorphous particles.

Figure 1 also shows the XRD pattern of sodium silicate/SnFe$_2$O$_4$ samples which are prepared through the combination of sodium silicate in solution form with SnFe$_2$O$_4$ nanoparticles with a ratio of 0.5, 1, and 2% w/w. In all of the patterns sodium Silicate with the formula of Na$_2$SiO$_3$ shows hexagonal structure (Ref. code: 00-016-0818) with the characteristic peaks of 16.8, 24.9, 29.3, 34.8, 37.2, 45.5, 48.1, 49.4, 52.0, 64.1, and 65.7 [2θ°].

The morphology of the synthesized nanoparticles was studied through the FESEM test (Figure 2). Observations show that homogeneous spherical nano-particles of SnFe$_2$O$_4$ with dimensions of less than 50 nm were formed. The images taken from mixed samples indicate the formation of almost homogeneous samples in which SnFe$_2$O$_4$ nanoparticles are distributed homogeneously in the sodium silicate structure.

First the preparation of 5-amino-2,4-dioxo-7-phenyl-2,3,4,4a,7,7a,8,9,10,11-decahydro-1H-benzo[i]quinazoline-6-carbonitrile (1d) through the four-component reaction of cyanoacetamide, cyclohexanone, and benzaldehyde using NaOH and Na$_2$SiO$_3$ as basic catalysts under solvent-free conditions (100°C) was investigated (Table 1). Na$_2$SiO$_3$ shows a higher yield (Table 1, entry 2). By increasing the temperature to 130°C, the product yield was increased up to 75% (Table 1, entry 3). Subsequently, SnFe$_2$O$_4$ nano-particles were added to sodium silicate with three different ratios as 0.5, 1, and 2% w/w. The catalytic activity of three samples was examined under solvent and solvent-free conditions and the results are summarized in Table 1 (entries 4-11). The results show that solvent suppressed the reaction process and all solvent media are inferior and no product yield was formed. Notably, the addition of SnFe$_2$O$_4$ nano-particles increased the productivity of Na$_2$SiO$_3$ in solvent-free conditions. The higher yield was achieved when sampling with 2% w/w of SnFe$_2$O$_4$ nanoparticles was used. Finally, Na$_2$SiO$_3$ containing 2% w/w of SnFe$_2$O$_4$ was selected as the most effective catalyst for the preparation of 1d.

The effect of catalyst dosage on the product yield is shown in Table 1. Accordingly, the reaction of cyanoacetamide, cyclohexanone and benzaldehyde was
Figure 1: XRD patterns of pure SnFe$_2$O$_4$ nanoparticles and sodium silicate/SnFe$_2$O$_4$ mixture with a ratio of 0.5, 1, and 2% w/w of SnFe$_2$O$_4$/sodium silicate.

Figure 2: FE-SEM images of Zn$_2$SnO$_4$ nanoparticles (a) and sodium silicate/SnFe$_2$O$_4$ mixture with a ratio of 0.5% w/w (b), 1% w/w (c), and 2% w/w (d) of SnFe$_2$O$_4$. 
investigated at 130°C in the presence of different amounts of catalyst (Na₂SiO₃ (with 2% of SnFe₂O₄)). The results show that 7.1% mol of the catalyst has the highest efficiency to produce a high yield of product 1d. No notable increase was done on the product yield with increasing the catalyst dosages to higher than 7.1% mol.

Temperature is one of the effective parameters on the productivity of multi-component reactions. Thus the reaction of cyanoacetamide, cyclohexanone, and benzaldehyde in the was investigated at different temperatures (Table 1). Giving access to 1d as the expected product is not effective at below 100°C. The reaction has a reasonable high yield at 130°C and no notable change in reaction yield was observed with further increasing of the reaction temperature. Finally, the optimum condition for the preparation of 1d was chosen as Na₂SiO₃ with 2% w/w of SnFe₂O₄ as catalyst (7.1% mol), temperature (130°C) and solvent-free condition.

Under the above-optimized conditions, the scope of the work was examined using various aromatic aldehydes substituted with different electron-donating and electron-withdrawing groups. The results are shown in Table 2. In all cases a series of 5-amino-2,4-dioxo-7-aryl-2,3,4,4a,7a,8,9,10,11-decahydro-1H-benzo[i]quinazoline-6-carbonitriles were synthesized in high yields (Table 2, entries 1d-5d). The procedure is flexible for structural modifications. In continue, the scope of the work was expanded using different cyclic ketones including cyclopentanone and tetrahydro-4H-thiopyran-4-one led to the synthesis of products 1e-7e, 1f-7f, and 1g-3g, respectively (Table 2).

Next, the reaction conditions were further modified and the reactions were performed under ultrasonic radiation conditions and high speed ball milling (HSBM) technique. In all reaction conditions, high yield products were obtained. Generally, aromatic aldehydes substituted at para and meta positions with halogen atoms show more reactivity compared to those of electron-donating groups (e.g. CH₃, OCH₃). ortho-Substituted aldehydes showed longer reaction times than their para-counterparts.

The proposed mechanism responds that the initiation of the reaction will include the Knoevenagel condensation reaction of cyanoacetamide with benzaldehyde and cyclohexanone to form 2-cyano-3-phenylacrylamide (1) and 2-cyano-2-cyclohexylideneacetamide (2) intermediates which can be catalyzed by Na₂SiO₃. Compound 2 reacts with a base to form an anion intermediate which subsequently undergoes a nucleophilic 1,4-addition to form 3. The next steps consisted of cyclization, intramolecular reactions, and finally 1,3-H shift to form the desired products (Scheme 2).

### Table 1: Preparation of 1d: catalyst and solvent screening, effect of catalyst dosage and temperature.

| Entry | Catalyst | Solvent (20 mL) | t (°C) | Time (h) | Yield (%) |
|-------|----------|-----------------|-------|----------|-----------|
| 1     | NaOH     | -               | 100   | 5        | 30        |
| 2     | Na₂SiO₃ (8.7% mol) | - | 100 | 5 | 35 |
| 3     | Na₂SiO₃ (8.7% mol) | - | 130 | 5 | 75 |
| 4     | A (7.1% mol) | - | 130 | 3 | 73 |
| 5     | B (7.1% mol) | - | 130 | 3 | 72 |
| 6     | C (7.1% mol) | - | 130 | 3 | 91 |
| 7     | C (7.1% mol) | EtOH | Reflux | 3 | - |
| 8     | C (7.1% mol) | DMF | Reflux | 3 | - |
| 9     | C (7.1% mol) | CH₃CN | Reflux | 3 | - |
| 10    | C (7.1% mol) | Toluene | Reflux | 3 | - |
| 11    | C (7.1% mol) | Ethylene glycol | 130 | 3 | - |
| 12    | C (7.1% mol) | - | 120 | 3 | 80 |
| 13    | C (7.1% mol) | - | 100 | 3 | 78 |
| 14    | C (7.1% mol) | - | 80 | 3 | - |
| 15    | C (1.9% mol) | - | 130 | 3 | 24 |
| 16    | C (13.4% mol) | - | 130 | 3 | 84 |
| 17    | C (16.1% mol) | - | 130 | 3 | 86 |

* Isolated yield – A: Na₂SiO₃ (with 0.5% w/w of SnFe₂O₄); B: Na₂SiO₃ (with 1% w/w of SnFe₂O₄); C: Na₂SiO₃ (with 2% w/w of SnFe₂O₄)
3 Conclusion

A mixture of Na₂SiO₃ with three different proportions of SnFe₂O₄ nano-particles was prepared, characterized by XRD, FE-SEM techniques and subsequently, was used for the preparation of 1d-5d, 1e-7e, 1f-7f, and 1g-3g in high yields. The high basic power of sodium silicate is decreased by adding SnFe₂O₄ nanoparticles which reduce the adverse reactions and disorientation, and increased the selectivity of the catalyst.

Experimental

The solvents, reactants and chemicals used in this study are from the Merck and Sigma-Aldrich Chemical Companies. The XRD patterns were taken in a PHILIPS PW3040 device. NMR spectra were recorded in a Bruker Avance DPX 400 MHz instrument in DMSO-d₆ as solvent relative to TMS (0.00 ppm). A Heraeus CHN-O-Rapid analyzer was used for elemental analysis. FE-SEM photographs are taken using the FEI NOVA NANOSEM 450 photographic apparatus.

Preparation of SnFe₂O₄ nanoparticles

Two different solutions were prepared. The first solution was made up of SnCl₂ (1 mmol) and FeCl₃·6H₂O (2 mmol) in 100 mL of ethanol. The second solution contains 20 mL ammonia in 40 mL of distilled water. The second solution is added slowly to the first solution under stirring. When the sedimentation process was completed, the solution is released for 30 min. The desired precipitate is then separated by a filter paper and washed with distilled water. Finally, the mixture was calcined at 500°C.

Preparation of SnFe₂O₄/sodium silicate powder

SnFe₂O₄ nanoparticles are added to a solution of sodium silicate (1g Na₂SiO₃ in 10 mL H₂O) with a ratio of 0.5% w/w SnFe₂O₄/sodium silicate and heated up to 100°C for
60 min, until a solid homogeneous mixture is obtained. Two additional samples was prepared with 1% and 2% w/w of SnFe$_2$O$_4$ by the same procedure.

Synthesis of 1H-benzo [i] quinazoline-6-carbonitrile derivatives

Method A:
A mixture of cyanoacetamide (3 mmol), cyclohexanone (1.2 mmol), benzaldehyde (1 mmol) and nanocatalysts (7.1% mol) are heated at 130°C until the reaction is complete (TLC monitoring). After completion of the reaction, the mixture is cooled to ambient temperature and mass was dissolved in hot ethanol and the insoluble catalyst is separated off by the filter paper. The resulting solution is concentrated until the evaporated solvent and sediments are recrystallized in cold watery ethanol and subsequently washed with diethyl ether to yield the pure product.

The reaction was also carried out with benzaldehyde derivatives.

Next, the reaction was carried out with all of the conditions described above with tetrahydro-4H-thiopyran-4-one (1.2 mmol) and cyclopentanone (1.2 mmol) instead of cyclohexanone.

Method B:
The mixture was ultra-sonicated at 120°C. The procedure is similar with method A.

Method C:
The mixture was milled at 120°C. The procedure is similar with method A.

The mixture was milled in a stainless steel grinding vial (10 mL volume) equipped with a stainless steel ball (diameter: 6 mm; mass: 1.04 g) for appropriate times at 25 Hz and 120°C.

Conflict of interest: There is no conflict of interest to be reported.

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