Gold nanoparticles (Au NPs) coupled with 3-morpholinopropylsulfonic acid (MOPS) for catalytic performance to the cyclocondensation reaction of aromatic/heteroaromatic/aliphatic aldehydes, indole and aromatic/heteroaromatic amines have been demonstrated for the first time in favour of 3-aminoalkylated indoles in ethyl alcohol at reflux temperature. Reaction conditions are just like ambient nevertheless all chemical transformations completed smoothly contributing worthwhile for the synthesis of 3-aminoalkylated indoles.

Keywords: Gold nanoparticles; catalytic performance; amino alkylated indoles; 3-morpholinopropylsulfonic acid (MOPS).

**INTRODUCTION**

In recent years, an emphasis of scientists and scientific communities is infusing to nurture the science and technology for human development and environment sustainability. For this accomplishment we need to use either clean and green recourses or processes or design such protocols that should not generate waste materials. In this regards, we proposed this permissive protocol that covers the green chemistry features.

Literature assessment revealed that nanocatalysts are successfully utilized for various organic transformations. Nanomaterials provide active surface area and having high surface to volume ratio. Hence, that accelerate rate of chemical transformation while reducing activation energy of reactants. Nanomaterials provide active surface area and having high surface to volume ratio. Hence, that accelerate rate of chemical transformation while reducing activation energy of reactants.

MOPS help to involve reacting precursors in the chemical reaction by protonating them at the appropriate site. Henceforth, coupled nanocatalyst that is Au-MOPS could be a dedicated catalyst for beneficent synthetic route to 3-amino alkylated indoles. Literally, several chemical, biochemical applications of MOPS have been found as it is an excellent buffer for many biological systems at near-neutral pH with a pKa of 7.20. Chemical structure of MOPS contains a morpholine ring having propane sulfonic acid as a substituent at nitrogen atom. Herein, this protocol acquires benefits of both Au NPs as well as MOPS as a coupled catalyst.

As we know in many natural products a pharmacodynamic nucleus of indole exhibited characteristic activities, therefore indole moiety gaining considerable importance. In particular, 3-C-functionalized indoles are highly applicable for the synthesis of various indole impurities in support of active pharmaceutical ingredients (APIs) such as antibacterial, anti-inflammatory and analgesic agent, anticonvulsant, cardiovasular, HIV-1 inhibitor, antimigraine and to cure breast cancer. Because of such widespread medicinal applications of 3-substituted indole nucleus the chemists and pharmacists are consistently engaged in the development of competent methodologies for proposed nucleus by applying several conditions such as β-cyclodextrin, Silver triflate (AgOTf), ionic liquids, indium/HCl, PMA-SiO2/CH3CN. Moreover, 3-substituted indoles via reactive intermediates alkylidene indoleamine have also been attempted through state of the art conditions with considerable yields of the product in hand.

Herein, we have proposed beneficent and user friendly synthetic route to the 3-aminoalkylated indole nucleus in the presence of Au-MOPS coupled catalyst in ethyl alcohol at reflux temperature.

**EXPERIMENTAL**

All the reagents and solvents were used for the reactions and column chromatography were purchased from HiMedia, Finechem, Spectrochem and Rankem Chemical Companies and used directly without further purification. The progress of the reactions was monitored by thin-layer chromatography 60 F254 (TLC). 1H NMR spectra were recorded on 300 MHz FT-NMR spectrometer in CDCl3 as a solvent and chemical shifts were reported in parts per million (ppm) relative to tetramethyl silane (CH3)4Si.

**Preparation of Au NPs**

Solutions of 0.025 M gold(III) chloride as a precursor and 0.5 M L-Ascorbic acid solution as a reducing and capping agent are prepared in a doubled distilled water. Gold(III) chloride solution is heated with continuous stirring on magnetic stirrer up to its boiling point. L-Ascorbic acid reducing agent is added drop by drop to the gold(III) chloride solution. Colour of the solution changes from colourless to ruby red indicates the formation of gold nanoparticles (Au NPs) which are cooled and stored in airtight glass container and used with MOPS as a catalyst for the said reaction.

**Characterization of Au NPs**

The UV-VIS absorption of gold nanoparticles was measured in single beam spectrophotometer and absorption maxima was noted.
at different wavelength (523-551 nm). The gold colloidal gold synthesis in experiment shown heavy absorption at 523 nm. Four runs taken of samples with different reducing agent which are L-ascorbic acid and trisodium citrate and different concentration of it were taken i.e. in limited and excess amount. Baseline for UV-Vis was distilled water.

The size of gold nanoparticles has been determined by measuring the diameter of whole particles on TEM images. The average diameter of colloidal gold was around 25 nm and minimum size being around 7 nm.

Preparation of 3-aminalkylated indoles

In hard glass test tube vanillin (0.306 g, 0.002 mol) and aniline (0.186 g, 0.002 mol) and MOPS (0.06 g, 1 mmol) in 25 mL ethyl alcohol was stirred at 60-65 °C for one hour. To this solution, Indole (0.234 g, 0.002 mol) was added portion wise with continued stirring at same temperature. The progress of the reaction was monitored after interval of each half hour by TLC. The reaction is completed after specified period of time. After completion the reaction mixture was poured on crushed ice, the obtained solid was filtered, dried and purified by column chromatography on silica gel using ethyl acetate/n-hexane solvent system to yield a pure product. Similar procedure was applied for the synthesis of other derivatives. All compounds were characterized by spectroscopic analysis.

### N-((1H-Indol-3-yl)(phenyl)methyl)benzeneamine (4a)

1H NMH (200 MHz, CDCl3): δ 9.95 (1H, s, NH), 7.90 (H, s, Ar-H), 6.7-7.5 (9H, m, Ar-H), 6.3-6.5 (5H, m, Ar-H), 5.85 (1H, s, C=H), 3.9 (1H, s, NH); 13C NMR (50 MHz, CDCl3): δ 144.14, 136.80, 128.88, 128.84, 128.33, 127.19, 126.24, 123.76, 122.01, 120.04, 119.80, 119.32, 111.17, 140.30; LC MS: m/z 298.15.

### N-((4-Chlorophenyl)(1H-indol-3-yl)methyl)benzeneamine (4b)

1H NMH (200 MHz, CDCl3): δ 10.09 (1H, s, NH), 5.34 (1H, s, C=H), 6.43–7.04 (5H, m, Ar-H), 7.01–7.38 (8H, m, Ar-H), 6.81 (1H, s, Ar-H), 3.95 (1H, s, NH); 13C NMR (50 MHz, CDCl3): δ 61.7, 111.1, 112.0, 113.3, 117.2, 118.9, 119.9, 122.1, 123.0, 127.1, 128.0, 128.5, 129.3, 132.9, 136.4, 140.2, 147.5; LC MS: m/z 332.99.

### N-((4-Hydroxyphenyl)(1H-indol-3-yl)methyl)benzeneamine (4c)

1H NMH (200 MHz, CDCl3): δ 10.1 (1H, s, NH), 5.16 (1H, s, C=H), 6.43–7.04 (5H, m, Ar-H), 6.61–7.4 (8H, m, Ar-H), 6.43 (1H, s, Ar-H), 3.91 (1H, s, NH), 5.32 (1H, s, OH); 13C NMR (50 MHz, CDCl3): δ 145.30, 137.00, 130.80 (1H, s, NH), 5.61 (1H, s, OH); 13C NMR (50 MHz, CDCl3): δ 10.80 (1H, s, NH), 5.61 (1H, s, C=H), 6.47–7.40 (13H, m, Ar-H), 6.71 (1H, s, Ar-H), 4.05 (1H, s, NH), 2.85 (6H, s, C=H); 13C NMR (50 MHz, CDCl3): δ 40.3, 61.9, 110.19, 111.9, 113.5, 142.1, 117.1, 119.3, 120.3, 122.1, 123.0, 127.1, 128.0, 128.5, 129.3, 131.9, 136.4, 147.9; LC MS: m/z 341.17.

### N-((1H-Indol-3-yl)(phenyl)methyl)benzeneamine (4d)

1H NMH (200 MHz, CDCl3): δ 10.00 (1H, s, NH), 7.40 (1H, s, Ar-H), 6.7–7.5 (5H, m, Ar-H), 6.3–6.5 (4H, m, Ar-H), 5.15 (1H, s, C=H), 4.0 (1H, s, NH), 1.90 (3H, s, CH3); 13C NMR (50 MHz, CDCl3): δ 145.30, 137.00, 130.50, 123.20, 123.00, 119.40, 114.05, 55.40, 23.01; LC MS: m/z 236.17.

### N-((1H-Indol-3-yl)(phenyl)methyl)benzeneamine (4j)

1H NMH (200 MHz, CDCl3): δ 8.99 (1H, s, NH), 6.90 (1H, s, Ar-H), 6.24–7.08 (8H, m, Ar-H), 7.18–7.5 (4H, m, Ar-H), 5.45 (1H, s, C=H), 4.2 (1H, s, NH); 13C NMR (50 MHz, CDCl3): δ 65.2, 106.80, 110.08, 111.84, 112.33, 127.19, 113.24, 117.06, 119.01, 120.04, 122.80, 122.92, 127.17, 129.30, 136.5, 142.1, 147.5, 152.50; LC MS: m/z 288.15.

### N-((Furan-2-yl)methyl)(1H-indol-3-yl)(phenyl) methanamine (4k)

1H NMH (200 MHz, CDCl3): δ 10.05 (1H, s, NH), 6.90 (1H, s, Ar-H), 6.7–7.14 (12H, m, Ar-H), 5.19 (1H, s, C=H), 2.50 (1H, s, NH); 13C NMR (50 MHz, CDCl3): 47.2, 58.9, 106.19, 111.9, 112.5, 119.2, 120.1, 122.1, 123.0, 127.1, 128.0, 128.6, 136.5, 148.8; LC MS: m/z 320.15.
RESULTS AND DISCUSSION

Gold NPs were prepared in the reaction of a hot 0.025 M gold(III) chloride as a precursor and 0.5 M L-ascorbic acid solution as a reducing and capping agent added dropwise. The UV spectra of ruby-red solution indicates the formation of gold nanoparticles (Au NPs). UV-VIS spectrophotometry is an important method in characterizations of gold nanoparticles. With increase in particle size the absorption peak shifts to longer wavelength and the width of absorption spectra is related to size distribution range. Generally gold nanoparticles display a single absorption peak in visible range between 510-550 nm this gives ruby red color to gold nanoparticles which varies according to their size.

If coagulation is not permitted, the nuclei formed at the earliest time will grow to the largest size, and no particle can be larger than that. The particle size distribution result shows the size of nanoparticles in the solution with average size of 28 nm.

Coagulation leads to formation of larger particles, and hence, the size distribution has become broader which is reflected in the Figure 3.

Table 1. Screening of catalyst concentration for the synthesis of 3-aminoalkylated indoles

| Sr. No | Catalyst (mmol) in 20 mL Au NPs solution | Time, h | Yield, % |
|--------|-----------------------------------------|---------|----------|
| 1      | 0.4                                     | 8.5     | 55       |
| 2      | 0.6                                     | 8.5     | 62       |
| 3      | 0.8                                     | 8.5     | 70       |
| 4      | 1.0                                     | 8.5     | 85       |
| 5      | 1.2                                     | 8.5     | 85       |

Reaction conditions: vanillin (0.306 g), aniline (0.234 g), indole (0.186 g) and MOPS (0.06 g) stirred at reflux temperature.

Table 2. Selection of suitable solvent for the synthesis of 3-aminoalkylated indoles

| Sr. No | Solvent            | Time, h | Yield, % |
|--------|--------------------|---------|----------|
| 1      | Water              | 24      | 20       |
| 2      | Methanol           | 10      | 65       |
| 3      | Isopropyl alcohol  | 15      | 60       |
| 4      | Amyl alcohol       | 15      | 20       |
| 5      | Ethyl alcohol      | 8.5     | 85       |
| 6      | Aqueous Alcohol (1:1) | 15 | 45       |
| 7      | Acetone            | 10      | 68       |

Reaction condition: vanillin (0.306 g), aniline (0.234 g), indole (0.186 g) and MOPS (0.06 g) stirred at reflux temperature.
Keeping the sustainability aspects in mind we screened various solvents for the model reaction we found that ethyl alcohol is the best solvent for the sake of yield of the product, easy work-up, water soluble solvent and user friendly nature (Table 2).

With this examination Au-MOPS in ethyl alcohol was used to synthesize 3-aminoacylated indoles from aromatic/heteroaromatic/aliphatic aldehydes, aniline and indole (Table 3).

We started the reaction by addition of MOPS in the alcoholic solution of vanillin and aniline. After stirring this reaction mixture at reflux temperature for one hour yellow colored precipitation observed, that indicates formation Schiff’s base followed by condensation reaction. Thence, to this reaction mixture we added calculated amount of indole portion wise with continued stirring at same temperature. After two hours red colored precipitation observed in the reaction vessel that confirms formation of targeted product commenced. After each half hour reaction was monitored by TLC. After successful derivatization it has been observed that, there is no remarkable substituent effect. Both ring activating and deactivation substituted precursors reacted smoothly and resulted into the good to the better yield of the products.

To launch the scope and generality of the reaction aromatic aldehydes with electron donating and electron withdrawing substituent at different positions to the aromatic ring reacted smoothly and give a good to best yield of the product. Alongside, the heteroaromatic aldehydes are also proved to be amenable to these reaction conditions and did not show significant effect on the yield and reaction time. On the other hand, aliphatic aldehyde resulted comparatively less yield and took more time for transformation. The formation of products was confirmed by their physical constant and structures were elucidated by spectroscopic analysis.

**CONCLUSIONS**

We have developed a straight forward, beneficent and user friendly synthetic protocol for pharmacodynamic 3-aminoacylated indoles favored by gracious catalyst Au-MOPS coupled catalyst in ethyl alcohol. Au NPs have a substantial percentage of atoms on the surface that become an advantage to bound reactants less tightly on its surface and could easily detaches from the products. This synthetic strategy also covers the advantages of one-pot multicomponent transformations which will make this research work practically and economically feasible and provides foresight for sustainability.

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