Au-MOPS(3-MORPHOLINOPROPANE-1-SULFONIC ACID) COUPLED CATALYST FOR THE SYNTHESIS OF 3-AMINOALKYLATED INDOLES

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Gold nanoparticles (Au NPs) coupled with 3-morpholinopropane-1-sulfonic 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.

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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.[1,2] 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.[3-6] 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 [7-10] at near-neutral pH with a pK_a 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.[11-13] 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,[14] anti-inflammatory and analgesic agent,[15] anticonvulsant,[16] cardiovascular,[17] HIV-1 inhibitor,[18] antimigraine and to cure breast cancer.[19] 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,[20] Silver triflate (AgOTf),[21] ionic liquids,[22] indium/HCl,[23] PMA-SiO_2/CH_3CN.[24] 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.[25] 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 $CDCl_3$ as a solvent and chemical shifts were reported in parts per million (ppm) relative to tetramethyl silane $(CH_3)_4Si$.

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-aminoalkylated 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 (0.234g, 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-((1*H*-Indol-3-yl)(phenyl)methyl)benzeneamine (4a)

^{1}H NMH (200 MHz, $CDCl_3$): δ 9.95 (1H, s, NH), 7.90(1H, s, Ar-H), 6.7-7.5 (9H, m, Ar-H), 6.3-6.5 (5H, m, Ar-H), 5.85 (1H, s, C3H), 3.9 (1H, s, NH); ^{13}C NMR (50 MHz, $CDCl_3$): 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, 40.30.LC MS: m/z 298.15.

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

^{1}H NMH (200 MHz, $CDCl_3$): 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),. ^{13}C NMR (50 MHz, $CDCl_3$): 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)(1*H*-indol-3-yl)methyl)benzeneamine (4c)

^{1}H NMH (200 MHz, $CDCl_3$): 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). ^{13}C NMR (50 MHz, $CDCl_3$): δ: 61.9, 110.9, 112.1, 113.5, 115.2, 118.9, 119.9, 121.8, 124.0,127.4, 127.9, 129.3, 134.9, 136.6, 147.6, 156.7; .LC MS: m/z 314.09.

N-((1*H*-Indol-3-yl)(p-tolyl)methyl)benzeneamine (4d)

^{1}H NMH (200 MHz, $CDCl_3$): δ 7.81 (1H, brs), 7.30 (2H, d, J = 8.0 Hz, Ar-H), 7.00-7.10 (7H, m), 6.90 (2H, t, J = 8.0 Hz), 6.79 (2H, t, J = 8.0 Hz), 6.40 (2H, brs), 5.71 (1H, brs), 2.39 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 142.16, 135.80, 135.19, 130.00, 129.8, 128.01, 123.32, 121.5, 120.00, 119.6, 119.00, 109.90, 40.70, 22.05; .LC MS: m/z 312.11.

N-((4-hydroxy,3-methoxyphenyl)(1*H*-indol-3-yl)methyl)-benzeneamine (4e)

^{1}H NMH (200 MHz, $CDCl_3$): δ 9.39 (1H, s, NH), 5.6 (1H, s, C-H), 6.5–7.2 (8H, m, Ar-H), 7.1–7.6 (4H, m, Ar-H), 6.70 (1H ,s, Ar-H), 4.41 (1H, s, NH), 5.49 (1H, s OH), 3.89 (3H, S, C-H) ^{13}C NMR (50 MHz, $CDCl_3$): δ: 57.01, 62.4, 111.9, 112.3, 113.1,113.8, 116.2, 117.9, 119.7, 120.4, 121.0, 122.0, 122.9, 127.9, 129.8, 135.8, 136.5, 144.0, 148.7, 152.0; .LC MS: m/z 344.20.

N-((3-Chlorophenyl)(1*H*-indol-3-yl)methyl)benzeneamine (4f)

^{1}H NMH (200 MHz, $CDCl_3$): 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),. ^{13}C NMR (50 MHz, $CDCl_3$): 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-((2-Chlorophenyl)(1*H*-indol-3-yl)methyl)benzeneamine (4g)

^{1}H NMH (200 MHz, $CDCl_3$): δ 10.80 (1H, s, NH), 5.61 (1H, s, C-H), 6.63–7.75 (13H, m, Ar-H), 6.11(1H ,s, Ar-H), 4.15 (1H, s, NH),. ^{13}C NMR (50 MHz, $CDCl_3$): 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-(Dimethylamino)phenyl)(1*H*-indol-3-yl)methyl)benzene-amine (4h)

^{1}H NMH (200 MHz, $CDCl_3$): δ 10.10 (1H, s, NH), 5.11 (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); ^{13}C NMR (50 MHz, $CDCl_3$): δ: 40.3, 61.9, 110.19, 111.9, 113.5, 114.2, 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-(1-(1*H*-Indol-3-yl)ethyl)benzeneamine (4i)

^{1}H NMH (200 MHz, $CDCl_3$): 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, C3H), 4.0 (1H, s, NH), 1.90 (3H, s, CH3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.30, 137.00, 130.50, 128.30, 123.20, 123.00, 119.40, 114.05, 55.40, 23.01; .LC MS: m/z 236.17.

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

^{1}H NMH (200 MHz, $CDCl_3$): 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); ^{13}C NMR (50 MHz, $CDCl_3$): 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)(1*H*-indol-3-yl)(phenyl)methanamine (4k)

^{1}H NMH (200 MHz, $CDCl_3$): 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); ^{13}C NMR (50 MHz, $CDCl_3$): 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 characterization 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.

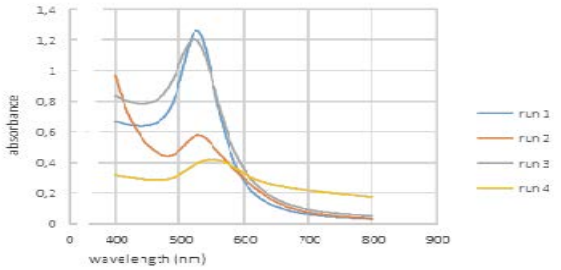


Figure1. UV-Visible absorbance spectra of Au NPs.

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.

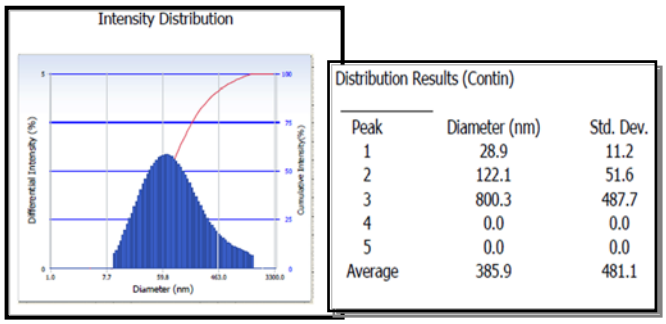


Figure 2. Particle size distribution (PSD) analysis of Au NPs.

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

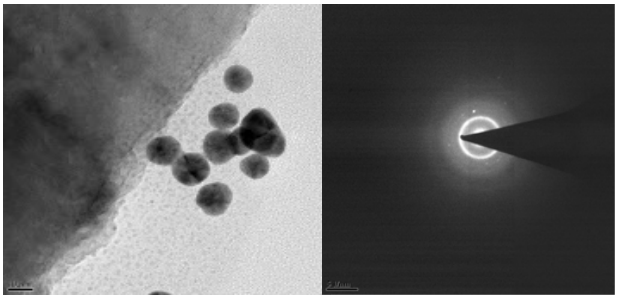
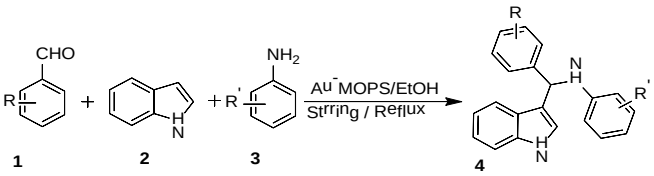


Figure 3. Transmission electron microscopy (TEM) image of as synthesized Au NPs at low magnification and its surface morphology of single Au NPS particle

In continuation of our previous efforts for the development of beneficent methodologies for the synthesis of various moieties [26] herein, at first attempt we tried the reaction of equimolar quantity of vanillin, aniline and indole in favour of MOPS and Au NPs in ethyl alcohol separately as a model reaction at room temperature as well as at reflux temperature on magnetic stirrer. But there was not considerable conversion of product we observed.

Further, while optimizing the reaction conditions and stoichiometry of catalyst concentration we coupled Au NPs and MOPS under ultrasonic condition in ethanol. We realized that coupling of Au-MOPS is really a suitable catalyst for the proposed transformation at reflux temperature (Scheme 1).



Scheme 1. Model reaction for 3-aminoalkylated indole.

Whereas, by considering the reaction time and product yield Au-MOPS were found to be the most capable catalyst. Au NPs provides active surface area on which all the reactants adsorbs chemically and MOPS initiates the reaction through ionic mechanism by protonating carbonyl oxygen so that condensation occurs between benzaldehyde and anilines to form imines intermediate. In 20 mL Au NPs solution following quantity (in mmol) of MOPS were added and the solutions were sonicated for 30 min. Which is then used as Au-MOPS catalyst for the screening of catalyst concentration and optimized concentration is further used for the synthesis of targeted products (Table 1).

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) stirred in ethyl alcohol (25 mL) 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.

Table 3. MOPS catalyzed synthesis of 3-aminoalcylated indoles

Entry	R/Aldehyde	R´/Amine	Time, h	Yield, %	M.P., °C
4a	H	H	8	85	180-182
4b	4-Cl	H	8	82	124-126
4c	4-OH	H	8	82	144-146
4d	4-CH_3	H	8	85	132-134
4e	4-OH, 3-OCH_3	H	8.5	85	163-165
4f	3-Cl	H	9	75	129-131
4g	2-Cl	H	8.5	80	128-130
4h	4-$N(CH_3)_2$	H	8	82	110-102
4i	Acetaldehyde	H	9	70	103-105
4j	Furfuraldehyde	H	8.5	78	140-142
4k	H	Furfurylamine	9	70	98-101

Reaction condition: vanillin (0.306 g); aniline (0.234 g); indole (0.186 g) and Au 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-aminoalkylated 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-aminoalcylated 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 practical and economically feasible and provides foresight for sustainability.

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