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Multicomponent synthesis of propargylamines in the presence of magnetic nanocatalyst

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In current study Fe_3O_4 nanoparticles have been used as a catalyst in the synthesis of propargylamines via three component reaction between aldehyde, alkyne, and an amine. The effect of different reaction parameters on conversion of aldehyde has been investigated and the samples have been characterized by appropriate techniques. It has been observed that in the presence of Fe_3O_4 nanoparticles and by applying microwave irradiation reaction time decreased significantly.

Keywords: Fe_3O_4 nanoparticles, Propargylamines, Multicomponent reaction, Catalyst

Separation is a very important unit process in chemical industries and in some cases has very high impact on final product cost. Separation of small particles such as used catalysts from the reaction medium by conventional methods is very difficult. Magnetic nanoparticles have been largely applied as a catalyst due to their high surface area, high dispersion, outstanding stability, and convenient separation and recycling[1,2]. In comparison with other separation methods such as cross-flow filtration or centrifugation, it is much easier to recover the catalyst from liquid-phase reactions by magnetic separation. The efficient separation of suspended magnetic catalyst from the product by applying an external magnetic field offers a solution for this problem. Magnetite (Fe_3O_4) nanoparticles are among the most common magnetic catalysts in the synthesis of organic compounds[3,4]. One of the most recent applications of Fe_3O_4 nanoparticles is in multicomponent reactions (MCRs) which are becoming an increasingly important class of reactions because they allow several starting materials to be combined, usually to form a single compound and in a one-pot operation[5–10]. These types of reactions exhibit an economy of steps and most of the incoming atoms are being linked together in a single product. Also MCRs can be applied as a powerful tool in the synthesis of biologically important compounds that decrease operative steps and enhance synthesis efficiency[11,12].

Propargylamines as a versatile class of compounds are extensively used as precursors in the preparation of heterocyclic compounds including quinolones[13], phenanthrolines[14], pyrroles[15], pyrrolidines[16], indolizines[17], or oxazolidinones[18,19]. Another application of them is their utilization as intermediates in the total synthesis of some natural and pharmaceutical products[20]. Also it was confirmed that some propargylamine derivatives can be potent anti-apoptotic agents that protect neurons against cell death in cellular and animal models of neurodegenerative disorders[21]. These derivates can also be used in the synthesis of many nitrogen containing biological active compounds, such as *b*-lactams, oxotremorine analogues, confirmationally restricted peptides, and isosteres[22]. In the classical methods of the synthesis of propargylamines strong bases such as butyl lithium[23], organomagnesium compounds[24] or LDA[25] are used in stoichiometric ratios which are mainly moisture sensitive and it is needed to control reaction conditions. Three-component coupling of an aldehyde, alkyne, and amine is one of the best examples of acetylene-Mannich MCR and has received much attention in recent years[26] in the synthesis of propargylamines. Various homogeneous metal catalyst including Cu(I) salts[27], Au(I)/Au(III) salts[28], Au(III) salen complexes[29], silver(I) salts[30], zinc salts[31], iron(III) salts[32], $InCl_3$ [33] and InBr[34] were applied for the C–H bond activation. AgI[35], Ag nanoparticles[36], Ni–Y–zeolite[37], copper ferrite nanoparticles[38] and Fe_3O_4 nanoparticles[39] are some examples of the heterogeneous catalysts for the synthesis of propargylamines from the three-component coupling reactions. Despite the advantages of homogeneous metal catalysts, their recovering problems from the reaction mixture severely inhibit their wide application in industry. But in the case of heterogeneous catalysts the opportunities for easy separation and recycling of the catalyst have increased demands of these types of catalysts. As a recoverable and magnetically separable catalyst, Fe_3O_4 has been applied in the synthesis of various types of organic compounds[40–42]. The development of new synthetic methods for the preparation of propargylamines remains an active research area. With these regards, it was intended in current study to synthesis propargylamines via coupling of an aldehyde, alkyne, and amine in the presence of the Fe_3O_4 nanoparticles which were synthesized by cyclic microwave approach. Also the effect of microwave irradiation in the synthesis of the propargylamines was investigated. It is possible to reach the products via fast and homogenous heating rate by this route[43–45]. Higher heating rate in comparison with conventional methods can solves temperature and concentration gradient problems[46]. When large amount of radiation is focused on reaction medium, charged particles receive a force from vibrating electric field and vibrate accordingly[46]. The vibration of reaction components has great effect on reaction progress and decrease time and power consumption significantly.

Materials and Methods

Materials and physical measurements

All the chemical reagents used in this experiment were of analytical grade and used as received without further purification. X-ray diffraction (XRD) pattern was obtained by a Philips- X'pertpro, X-ray diffractometer using Ni-filtered Cu Ka radiation. Field emission scanning electron microscopy (FESEM) images were obtained on TESCAN/MIRA equipped with an energy dispersive X-ray spectroscopy. ^{1}H-NMR spectra were recorded in duoterated acetone on a Bruker Advanced DPX 400 MHz spectrometer. To determine the purity of reaction products, a gas chromatograph (GC-MS), Agilent model 7890A with an HP-5 capillary column and an FID detector were used.

Preparation of Fe_3O_4 nanoparticles

Fe_3O_4 nanoparticles were synthesized according to our previous publication[47]. In summary for the synthesis of Fe_3O_4 nanoparticles 2 mmol of $Fe(NO_3)_3.9H_2O$ was dissolved in 15 mL of poly ethylene glycol 200 (PEG-200) under constant stirring and heating at 70 °C. Then a solution containing 5 mmol of NaOH in 15 mL PEG was added to the above solution and stirred for 10 min. The final solution was placed in a domestic oven, operating at 2.45 GHz, and exposed at 900 W of cyclic microwave (30 s on for every 60 s interval) for 6 min. Finally reaction component was cooled to room temperature and the black precipitate which were magnetically separable were collected and washed with ethanol and distilled water several times to remove impurity and unreacted materials and finally dried at 50 °C. To obtain well crystalline samples the final products were annealed at 200 °C for 5 h.

Typical procedure for A3-coupling reaction

A 5 mL round-bottomed flask was charged with aldehyde (0.5 mmol), secondary amine (0.6 mmol), and phenylacetylene (0.75 mmol) in acetone (2 mL). The reaction mixture was heated at 50–60 °C in oil bath under an argon atmosphere in the presence of 5 mol percent of Fe_3O_4 nanoparticles. When the reaction was completed (monitored by TLC) the solvent was evaporated under vacuum and the product was extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The crude product obtained was purified by column chromatography using ethyl acetate n-hexane (1:16) to afford the pure desired product. To investigate the rule of microwave irradiation on the conversion of the reaction components, the reaction was carried out at the same condition under microwave irradiation at different power and time. Example: N-(1,3-Diphenyl-2-propynyl)piperidine (Table 1, entry 1): ^{1}H-NMR δ = 7.00–7.65 (m, 10H), 4.80 (s, 1H), 2.40–2.60(m, 4H), 1.56–1.69 (m, 4H), 1.30–1.50 (m, 2H).

Results and discussion

XRD pattern of the synthesized nanoparticles is presented in Fig. 1. The crystallinity and phase

Table 1 — Catalyst concentration effect on A^3 coupling of aldehyde, alkynes and secondary amines by Fe_3O_4 nanoparticles as catalyst

Entry	Aldehyde (R^1)	Amine	Product	Time (h)	Catalyst (mol%)	Conversion (%)
1	C_6H_5-	Piperidine	P1	24	2.5	93.72
2	C_6H_5-	Piperidine	P1	24	5	99.71
3	C_6H_5-	Piperidine	P1	24	10	99.81

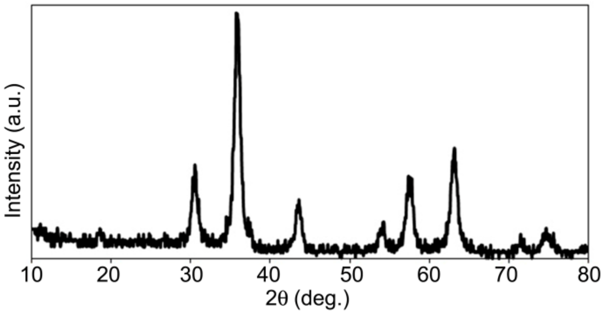


Fig. 1 — XRD pattern of Fe_3O_4 nanoparticles.

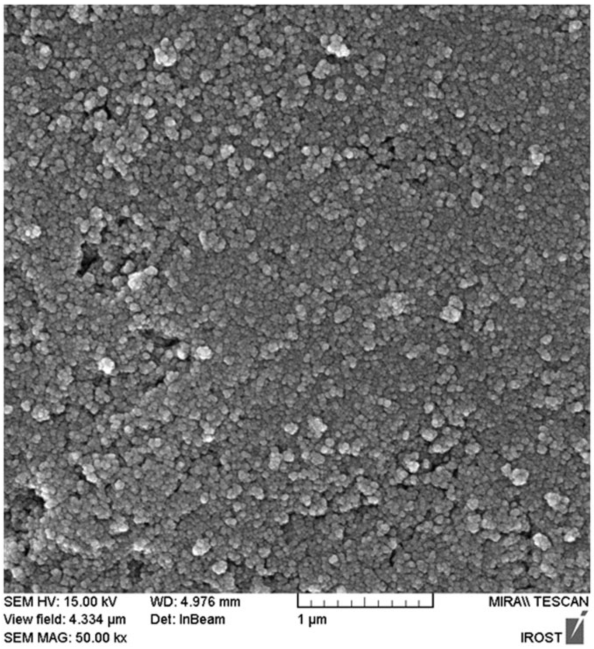


Fig. 2 — SEM image of Fe_3O_4 nanoparticles.

structure of the as synthesized sample are confirmed and can be attributed to the tetragonal structure of Fe_3O_4 which are very close to the values in the literature (JCPDS No. 88-0315).

SEM image of the synthesized Fe_3O_4 nanoparticles via microwave route as discussed before[47] are shown in Fig. 2. It is found that the synthesized nanoparticles are homogeneous and have uniform size distribution with average size distribution about 19–21 nm. It was also confirmed by EDS analysis (Fig. 3) that the nanoparticles are mainly composed of Fe and O which their ratio is close to 3:4. The presence of Au is attributed to coating of the particles for SEM analysis.

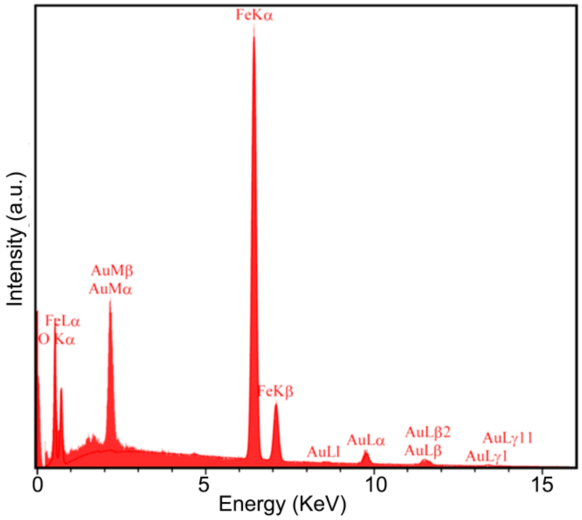
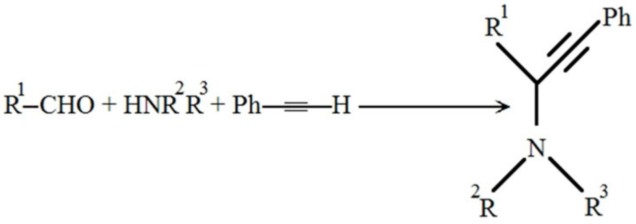


Fig. 3 — EDS analysis of Fe_3O_4 nanoparticles.



Schematic view of reaction.

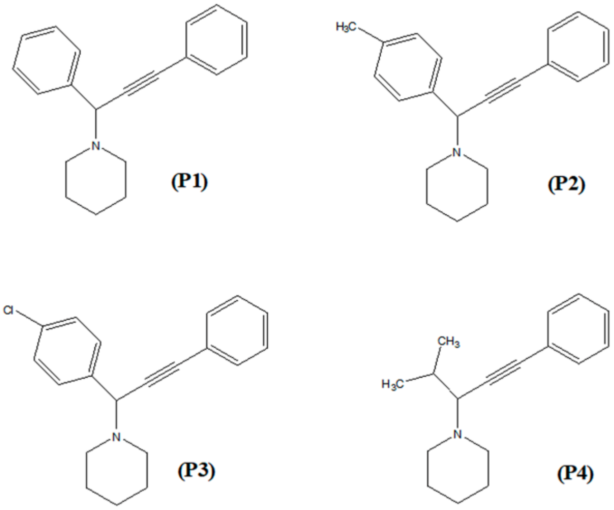
Scheme 1

To evaluate the catalytic activity of Fe_3O_4 nanoparticles initially on the traditional Mannich reaction, benzaldehyde, piperidine and phenylacetylene with above mentioned ratio in acetone were mixed and stirred under an argon atmosphere at 55 °C in the presence of 2.5 mol% of Fe_3O_4 nanoparticles for 24 h (Scheme 1). 93.72% conversion of benzaldehyde was found on the basis of GC analysis of the crude reaction mixture. Increasing the loading of Fe_3O_4 nanoparticles up to 5 mol% gave desired propargylamine (Table 1, entry 2) with 99.71% conversion. However, it was observed that the increase in the concentration of catalyst not only promotes the reaction but also leads to an increase of the yield. When the catalyst concentration was increased to 10 mol% there was no significant changes in conversion and with this regards 5 mol% was chosen as an optimum catalyst concentration. The products structures can be found in Scheme 2.

Applying of acetone as solvent influenced not only the coupling reaction of aldehyde, alkyne, and amine in good yield, but also performed well in the process of magnetic separation of nanoparticle catalysts, by decreasing the viscosity of the reaction mixture and facilitating the congregation of magnetic catalyst, when the reaction was completed.

The effect of different functional groups on the reaction and conversion of the aldehyde was investigated and the results are presented in the Table 2. As can be seen in the presence of electron withdrawing groups reaction yield was decreased while in the case of electron donating groups no significant changes were observed in the reaction yield.

All of the reactions were repeated at 12 and 6 h to investigate the effect of functional groups (Table 3). It was observed that aldehyde conversion was significantly decreased when reaction time decreased. In the case of electron withdrawing groups this conversion was significantly decreased in comparison with those reactions at 24 h. Also it was seen that there are no significant differences in the conversion of the aromatic and aliphatic aldehydes.



Products structures.
Scheme 2

By considering of these results and literature reports[48–50] a plausible mechanism was proposed as shown in Scheme 3. Fe_3O_4 has cubic inverse spinel crystal structure which the oxygen anions form a closely packed face-centered cubic (fcc) sublattice with iron cations located in interstitial sites. Two different kinds of cation sites exist in Fe_3O_4: tetrahedrally coordinated sites occupied by Fe^{3+} and octahedrally coordinated sites occupied by Fe^{3+} and Fe^{2+} ions in equal numbers[46]. The Fe^{2+} cation can be considered to be Fe^{3+} plus an ‘extra’ electron, with rapid valence oscillation between the Fe(III) and Fe(II) octahedral sites. At first deprotonation of terminal alkyne occurs in the presence of amine which leads to the activation of C–H bond and terminal iron-acetylide intermediate (I) forms that could be presumably due to the reduction of Fe^{3+} to a low valent Fe^{2+} oxidation state. Iron cations are considered as Lewis acid which increase the electrophilic character of the starting aldehyde and stabilize the immonium salt by the coordination of the oxygen or nitrogen lone pair[51]. The formed iron-acetylide intermediate (I), further undergoes nucleophilic addition to the immonium ion (II), to yield the corresponding propargylamine (III) and regeneration of the catalyst[49].

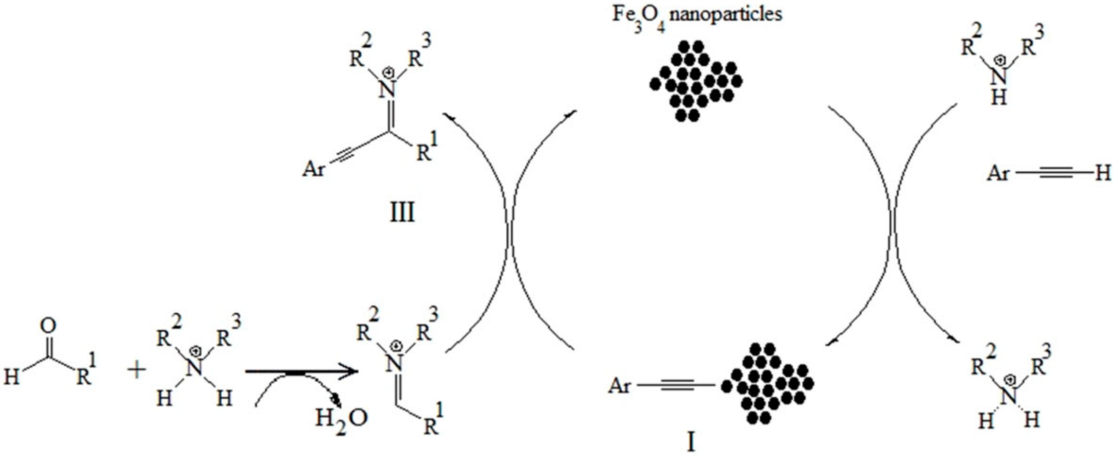
The reaction was carried out again in the presence of microwave irradiation at different irradiation powers and times (Table 4). It was observed that by increasing of microwave irradiation power aldehyde conversion is

Table 2 — The effect of functional groups on A^3 coupling of aldehyde, alkynes and secondary amines

Entry	Aldehyde (R^1)	Amine	Product	Time (h)	Catalyst (mol%)	Conversion (%)
4	4-MeC_6H_4-	Piperidine	P2	24	5	99.52
5	4-ClC_6H_4-	Piperidine	P3	24	5	93.84
6	Isobutyraldehyde	Piperidine	P4	24	5	99.74

Table 3 — The effect of reaction time and functional groups on A^3 coupling of aldehyde, alkynes and secondary amines

Entry	Aldehyde (R^1)	Amine	Product	Time (h)	Catalyst (mol%)	Conversion (%)
7	C_6H_5-	Piperidine	P1	12	5	93.84
8	C_6H_5-	Piperidine	P1	6	5	89.44
9	4-MeC_6H_4-	Piperidine	P2	12	5	92.20
10	4-MeC_6H_4-	Piperidine	P2	6	5	79.60
11	4-ClC_6H_4-	Piperidine	P3	12	5	72.43
12	4-ClC_6H_4-	Piperidine	P3	6	5	57.48
13	Isobutyraldehyde	Piperidine	P4	12	5	91.33
14	Isobutyraldehyde	Piperidine	P4	6	5	88.44



Reaction mechanism.

Scheme 3

Table 4 — The effect of microwave irradiation on A^3 coupling of aldehyde, alkynes and secondary amines

Entry	Aldehyde (R^1)	Amine	Power (W)	Time (min)	Catalyst (mol%)	Conversion (%)
15	C_6H_5-	Piperidine	300	2	5	-
16	C_6H_5-	Piperidine	600	2	5	33.57
17	C_6H_5-	Piperidine	900	2	5	42.37
18	C_6H_5-	Piperidine	900	30	5	87.54
19	C_6H_5-	Piperidine	900	60	5	99.33

increased. The same trend was seen in the case of elevating of reaction time. By simple comparison between those results obtained by microwave and conventional method, it can be concluded that by applying microwave irradiation as heating source it is possible to reach the same conversion of aldehyde at lower reaction time. When microwave irradiation power was 900 W, 99.81% of aldehyde was converted to the product at 60 min as shown in Table 4.

Despite the fact of the small amount of catalyst was applied (12 mg) it is worth mentioning that it could easily be recovered by a magnet (after addition of 10 mL of ethyl acetate n-hexane) and reused. Good catalyst performance in the coupling of benzaldehyde, piperidine, and phenylacetylene was observed over seven consecutive cycles without any significant loss of catalytic activity. In comparison with similar works, reaction yield and aldehyde conversion was increased in current investigation as shown in Table 5. The increase of conversion in current study can be attributed to the smaller size of the Fe_3O_4 nanoparticles in comparison with the same works.

Table 5 — A^3 coupling of aldehyde, alkynes and secondary amines by other catalysts in literature

Catalyst	mol%	Time (h)	Temp (°C)	Solvent	Conversion	Ref
Cu	10	24	70	-	49	[52]
CuO	10	24	70	-	55	[52]
Cu_2O	10	24	70	-	63	[52]
CuCl	10	24	70	-	80	[52]
$CuCl_2$	10	24	70	-	76	[52]
Au	10	12	75-80	MeOH	66	[53]
$NiCl_2$	5	8	80	Toluene	60	[54]
$NiCl_2$	5	8	100	Toluene	80	[54]
Fe_3O_4	20	16	65	MeOH	60	[55]

Conclusions

The synthesis of propargylamines via the traditional Mannich reaction of benzaldehyde, piperidine, and phenylacetylene was performed in current investigation and the effect of reaction parameters on the aldehyde conversion was investigated. It was observed that in comparison with other similar work, by applying such Fe_3O_4 nanoparticles as catalyst aldehyde conversion was increased significantly and in the presence of microwave irradiation reaction time decreased to 1 h. Overall current method offers advantages of recyclability of the catalyst with no significant loss of catalytic activity; ready availability which can be used or reused without further purification. This route requires lower catalyst loading and has broad substrate applicability, gives high yields in short reaction times, and is simple and easy to carry out. Also no additives or cofactor are needed making this procedure more environmentally acceptable.

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