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On-water magnetic $NiFe_2O_4$ nanoparticle-catalyzed Michael additions of active methylene compounds, aromatic/aliphatic amines, alcohols and thiols to conjugated alkenes†

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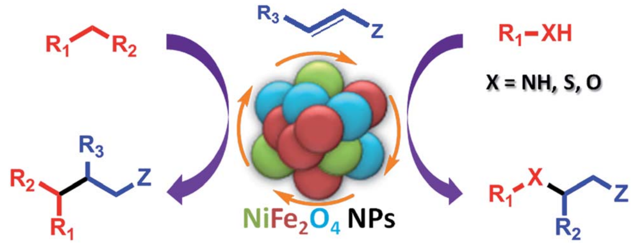
Here, we have demonstrated the Michael addition of active methylene compounds, aromatic/aliphatic amines, thiols and alcohols to conjugated alkenes using magnetic nano-$NiFe_2O_4$ as reusable catalyst in water. Nano-$NiFe_2O_4$ efficiently catalyzed the formation of C–C and C–X (X = N, S, O *etc.*) bond through 1,4-addition reactions.

The designing and vigilant utilization of catalysts can make an industrialized protocol economic, greener and more sustainable by reducing the formation of harmful waste to human health and the environment. The sustainability and applicability of the protocol can be enhanced by using water as solvent. Among other catalysts, the development of magnetic nanoparticles (MNP) paved the way on catalysis as well as in drug delivery, and remediation.[1,2] These MNP are robust, inexpensive, easily accessible and possess high surface to volume ratio. In addition, they added advantage of being separable by means of external magnet after completion of the reaction. Thus, introduction of MNPs as catalyst in useful organic transformations will be appreciated. However, literature study reveals that among these MNPs, $NiFe_2O_4$ nanoparticles (NPs) have extensively been used as supporting materials for active catalysts due to the high magnetic nature and robustness.[3,4] Interestingly, only few reports are present on the application of $NiFe_2O_4$ NPs in organic transformations.[5] As a part of our continuous effort in the field of nano-catalysis[6] recently, we have demonstrated the catalytic activity of nano-$NiFe_2O_4$ in transfer hydrogenation–dehydrogenation[6n] and in the synthesis of 2-alkoxyimidazopyridines.[6l]

On the other hand, the Michael addition is one of the most useful tool for the carbon–carbon (C–C; so called classical Michael addition reaction) bond-forming reactions and has wide synthetic applications in organic synthesis.[7] Alternatively, carbon–heteroatom (C–X) bond formations *via* aza-Michael (X = N), thia-Michael (X = S), oxa-Michael (X = O) addition reactions have attracted more attention due to wide applications in synthesis of variety natural products, antibiotics and other nitrogen, oxygen, sulphur containing bio-molecules.[8,9] Various catalysts including strong bases, Lewis acids, metal complexes, and oxides have been used for C–C and C–X Michael addition reactions[10–13] that often lead to undesirable side reactions,[14] and most of these catalysts were homogeneous in nature. However, there is a lack of common method using a robust and reusable catalyst to carry out the C–C and C–X Michael addition reactions. In this paper, we have demonstrated general protocol for the carbon–carbon and carbon–heteroatom bond formation *via* Michael addition reactions using nano-$NiFe_2O_4$ as reusable catalyst in water (Scheme 1).

To accomplish this research, initially, we have prepared $NiFe_2O_4$ NPs by following our previously reported method[6l] *via* sol–gel method (see ESI 1 for detailed procedure†). The powder X-ray diffraction (XRD) pattern (Fig. 1) of the prepared material reveals the formation of face centred cubic spinel $NiFe_2O_4$ (ref. 15) where the Bragg reflection peaks were indexed to *Fd*3*m* space group (JCPDS file no. 10-0325). The broadening of peaks indicates the formation of nano-particulate $NiFe_2O_4$ (average size ∼ 16 nm, calculated from Scherrer formula using XRD plane 440). The formation of spherical $NiFe_2O_4$ NPs with average particle sizes of 15 nm was also evident from high



Scheme 1 $NiFe_2O_4$ NPs catalyzed Michael addition reactions.

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† Electronic supplementary information (ESI) available: Detailed experimental procedure and characterization of catalyst and Michael addition; copies of ^1H and ^{13}C NMR of the products listed in Tables 2–5, reusability of $NiFe_2O_4$. See DOI: 10.1039/c6ra21160g

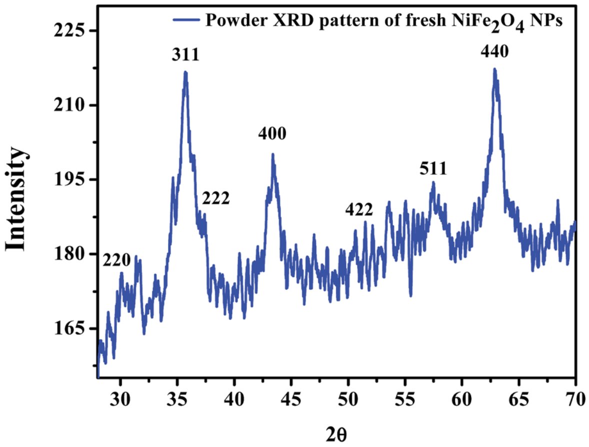


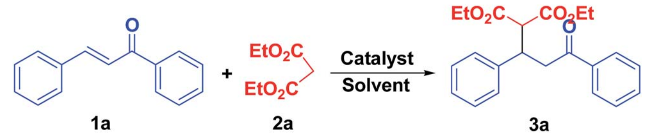
Fig. 1 The powder XRD pattern of nano-$NiFe_2O_4$.

resolution transmission electron microscopic (HRTEM) image (Fig. 2).

Next, we have attempted C–C Michael addition by the reaction of 1,3-diphenyl-prop-2-ene-1-one (**1a**, 1 mmol) and diethylmalonate (**2a**, 1.2 mmol) using nano-$NiFe_2O_4$ (10 mg) in water–ethanol mixture (1 : 1; 2 mL). It was observed good yield of Michael adduct (**3a**) isolated after 1 h (entry 1, Table 1). To establish the superiority of nano-$NiFe_2O_4$ we have carried out the same reaction with different catalysts. It was observed that Fe_3O_4 NPs, NiO NPs and $CuFe_2O_4$ could initiate the Michael addition reaction but the yields were very less (entries 2–4, Table 1) but other ferrites like, $ZnFe_2O_4$, $MgFe_2O_4$ and $CoFe_2O_4$, were found to be inactive in the reaction (entries 5–7, Table 1).

It was observed that only 10 mg of nano-$NiFe_2O_4$ was sufficient to carry out the reaction smoothly and yield remained same when the catalyst loading was increased to 15 mg (entry 8, Table 1). However, decreasing the catalyst amount to 5 mg, the yield of product decreased (entry 9, Table 1). The screening of solvents for the reaction it was observed that water–ethanol mixture and toluene (entry 10) gave the better results compared to other solvents tested here (entries 11–14, Table 1). Thus, 10 mg of nano-$NiFe_2O_4$ for 1 mmol of substrates in 2 mL of water–ethanol mixture (1 : 1) at 100 °C was considered as optimum reaction conditions.

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	Temperature	Time	Yield[b] (%)
1	$NiFe_2O_4$ NPs	H_2O : EtOH	100 °C	1 h	93
2	Fe_3O_4 NPs	H_2O : EtOH	100 °C	1 h	43
3	NiO NPs	H_2O : EtOH	100 °C	1 h	51
4	$CuFe_2O_4$ NPs	H_2O : EtOH	100 °C	1 h	30
5	$ZnFe_2O_4$ NPs	H_2O : EtOH	100 °C	1 h	Nd
6	$MgFe_2O_4$ NPs	H_2O : EtOH	100 °C	1 h	Nd
7	$CoFe_2O_4$ NPs	H_2O : EtOH	100 °C	1 h	Nd
8	$NiFe_2O_4$ NPs	H_2O : EtOH	100 °C	1 h	94[c]
9	$NiFe_2O_4$ NPs	H_2O : EtOH	100 °C	1 h	52[d]
10	$NiFe_2O_4$ NPs	Toluene	100 °C	1 h	94
11	$NiFe_2O_4$ NPs	DMF	100 °C	1 h	43
13	$NiFe_2O_4$ NPs	DCM	100 °C	1 h	48
14	$NiFe_2O_4$ NPs	DCE	100 °C	1 h	50

[a] Reactions were carried out with 1,3-diphenyl-prop-2-ene-1-one (1 mmol) and diethylmalonate (1 mmol) and 10 mg of $NiFe_2O_4$. [b] Yield of isolated product. [c] 15 mg of $NiFe_2O_4$. [d] 5 mg of $NiFe_2O_4$ was used.

Using optimized reaction conditions and following a simple experimental procedure[16] (detailed procedure provided in ESI 7†) we have explored the scope of the Michael addition reaction. We have observed that various active methylene compounds were smoothly reacted with conjugated alkenes such as conjugated ketones/carboxylic esters/nitriles under the optimized reaction conditions producing excellent yields of Michael adduct within short reaction time (0.5–1.5 h). The results were presented in Table 2. All the reactions listed in Table 2 are very clean and high yielding (89–98%). After the completion of reaction the nano-$NiFe_2O_4$ catalyst was separated simply by an external magnet and the product was extracted with ethyl acetate. The $NiFe_2O_4$ NPs were washed with water and ethanol respectively, dried and reused for subsequent reactions. The reusability of nano-$NiFe_2O_4$ was investigated for the Michael addition of 1,3-diphenyl-prop-2-ene-1-one (1.0 mmol; 208 mg) and diethylmalonate (1.2 mmol; 192 mg) as model reaction.

It was observed that nano-$NiFe_2O_4$ was very stable under the reaction conditions and little loss of yields were observed even after 10th cycle (Fig. 3).

Next, we have applied nano-$NiFe_2O_4$ in aza-Michael reaction of aromatic/aliphatic amines to conjugated alkenes. The aza-Michael addition of aliphatic amines is more facile than aromatic amines due their poor nucleophilicity and strong basic or fancy/expensive catalysts are required to initiate the reaction.

Here, nano-$NiFe_2O_4$ showed excellent catalytic activity towards aza-Michael addition of aromatic amines to conjugated

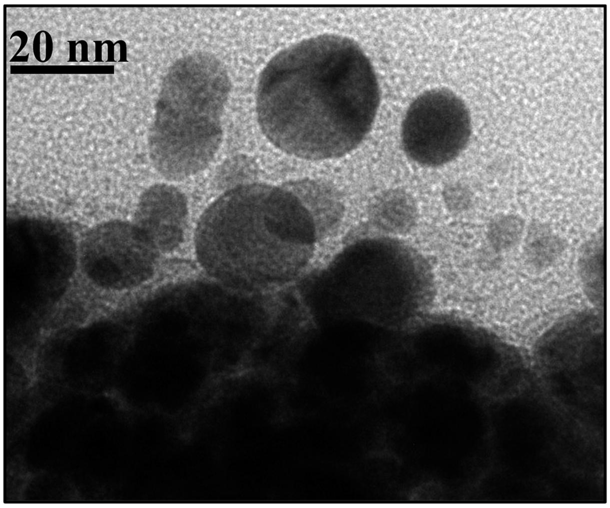
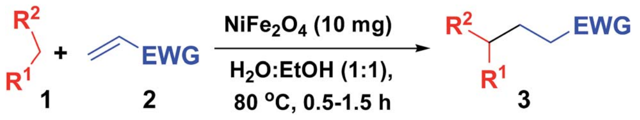
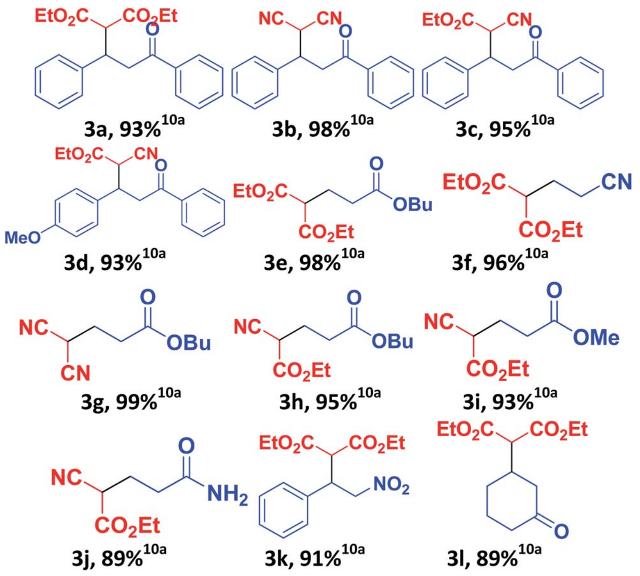


Fig. 2 The TEM image of nano-$NiFe_2O_4$.

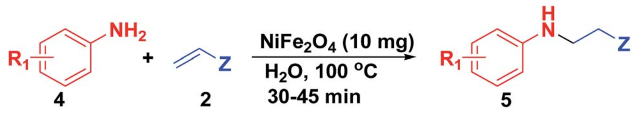
Table 2 Classical Michael addition reaction[a,b]

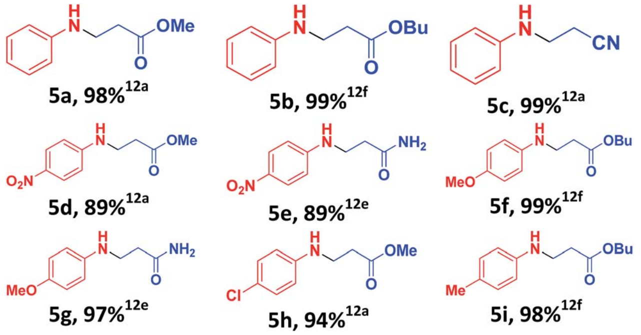



3a, 93%[10a]
3b, 98%[10a]
3c, 95%[10a]
3d, 93%[10a]
3e, 98%[10a]
3f, 96%[10a]
3g, 99%[10a]
3h, 95%[10a]
3i, 93%[10a]
3j, 89%[10a]
3k, 91%[10a]
3l, 89%[10a]

[a] Reaction conditions: active methylene compound (1.2 mmol), Michael acceptor (1.0 mmol), $NiFe_2O_4$ NPs (10 mg) in water–EtOH (1 : 1) mixture 2 mL at 100 °C for 1.5 h under air and R_f value in (9 : 1) petroleum ether and ethyl acetate mixture. [b] Yields refer to those of pure isolated products.

Table 3 Aza-Michael addition reaction with aromatic amine[a,b]




5a, 98%[12a]
5b, 99%[12f]
5c, 99%[12a]
5d, 89%[12a]
5e, 89%[12e]
5f, 99%[12f]
5g, 97%[12e]
5h, 94%[12a]
5i, 98%[12f]

[a] Reaction conditions: aromatic amine (1.0 mmol), Michael acceptor (1.5 mmol), 10 mg $NiFe_2O_4$ NPs at 100 °C in water and R_f value in (9 : 1) petroleum ether and ethyl acetate mixture. [b] Yields refer to those of pure isolated products.

alkenes in water. Thus, when a mixture of aniline (1 mmol; 93 mg), methyl acrylate (1.5 mmol; 129 mg) and nano-$NiFe_2O_4$ (10 mg) is refluxed in water (2 mL), methyl 3-phenyl propionate was obtained in excellent yield (176 mg; 98%). Aromatic amines with electron donating and electron withdrawing groups underwent conjugate addition to α,β-unsaturated ester, nitrile and amide under the optimized reaction conditions providing excellent yields (89–99%) of products (**5a–i**, Table 3). In addition to aromatic amines the nano-$NiFe_2O_4$ catalyst also enabled the aza-Michael addition of aliphatic amines to conjugated alkenes to produce Michael adducts (**7a–i**) at room temperature. The results were presented in Table 4. All the reactions were very fast (20–30 min) and high yielding (92–99%). The detailed experimental procedures have been provided in ESI 8 and 9.†

The excellent catalytic activity of nano-$NiFe_2O_4$ in classical Michael and aza-Michael addition reactions prompted us to explore its performance in the more challenging oxa-Michael

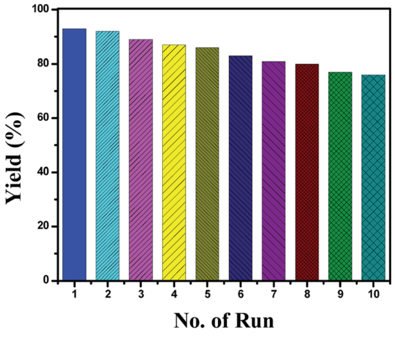
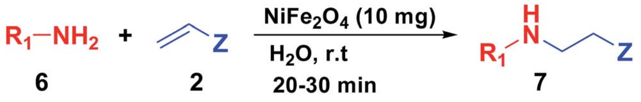
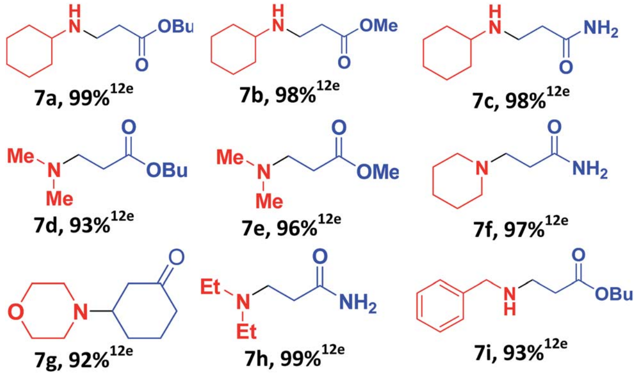


Fig. 3 Represents the reusability of nano-$NiFe_2O_4$ for the synthesis of diethyl 2-(3-oxo-1,3-diphenylpropyl)malonate (**3a**).

Table 4 Aza-Michael addition reactions of aliphatic amines to conjugated alkenes[a,b]




7a, 99%[12e]
7b, 98%[12e]
7c, 98%[12e]
7d, 93%[12e]
7e, 96%[12e]
7f, 97%[12e]
7g, 92%[12e]
7h, 99%[12e]
7i, 93%[12e]

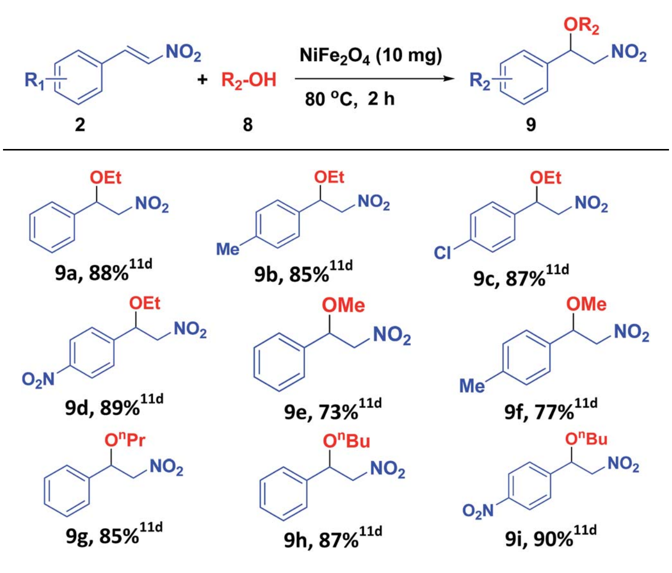
[a] Reaction conditions: aliphatic amine (1.0 mmol), Michael acceptor (1.5 mmol) in presence of 10 mg $NiFe_2O_4$ NPs under air at room temperature in water and R_f value in (9 : 1) petroleum ether and ethyl acetate mixture. [b] Yields of pure isolated products.

addition of aliphatic alcohol to conjugated alkenes. The nucleophilicity of alcohols are very poor due to electronegativity of oxygen atom. Interestingly, we have observed that nano-$NiFe_2O_4$ activated the alcohol to participate in oxa-Michael addition to β-nitrostyrene derivatives. Thus, when β-nitrostyrene (1 mmol; 149 mg) was refluxed with nano-$NiFe_2O_4$ (10 mg) in ethanol (2 mL), good yield (172 mg; 88%) of oxa-Michael adducts, 1-(1-ethoxy-2-nitroethyl)benzene was obtained after 2 hours (entry 1, Table 5). Here, ethanol act as nucleophile as well as solvent and no other solvent is required. The detailed procedure for the oxa-Michael addition has been given in ESI 10.† Various aliphatic primary alcohols such as ethyl alcohol, propyl alcohol and butyl alcohol were participated smoothly giving good yields (73–90%) of oxa-Michael adducts (**9a–i**, Table 5) with different β-nitrostyrenes. Both electron donating and electron withdrawing group present in the benzene ring of nitrostyrene were tolerated well in this reaction conditions. All the reactions are very clean, fast and high yielding (73–90%). The magnetic nano-$NiFe_2O_4$ catalyst was separated simply by using an external magnet and products were purified by short-column chromatography over silica gel.

In addition to the above mentioned Michael addition reactions, we have also applied nano-$NiFe_2O_4$ in Michael addition of aromatic thiol to conjugated ketones/carboxylic esters/nitriles and as expected the nano-catalyst provided excellent yields (86–99%) of thia-Michael adducts (**11a–f**, Table 6) within very short time period (10–15 minutes) in water at room temperature. The general experimental procedure has been provided in ESI 11.†

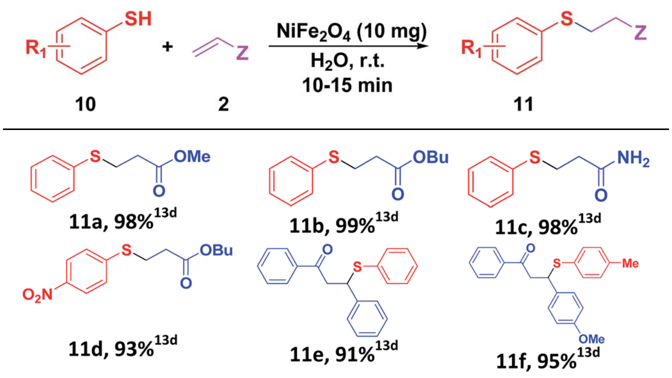
Finally, leaching study was performed to check the heterogeneity stability of the catalyst by hot filtration test for the synthesis of diethyl 2-(3-oxo-1,3-diphenylpropyl)malonate (**3a**). The catalyst, nano-$NiFe_2O_4$ was separated from reaction mixture (after 30 minutes associated with 30% conversion) by an external magnet under hot conditions and remaining mixture was continued to stir under standard reaction conditions for additional 2.0 h. However, no such significance improvement of yield of diethyl 2-(3-oxo-1,3-diphenylpropyl)malonate product was observed after separation of catalyst from the reaction mixture. The results were presented in Fig. 4. These results shows that the nano-$NiFe_2O_4$ catalyst was stable at the reaction conditions and apparently there was no leaching of metal content from NPs.

Table 5 Oxa-Michael addition of alcohols to conjugated alkenes[a,b]



[a] Reaction conditions: β-nitrovinyl benzene (1.0 mmol), aliphatic primary alcohols (2.0 mL), $NiFe_2O_4$ NPs (10 mg), at reflux for 2 h in open air and R_f value in (9 : 1) petroleum ether and ethyl acetate mixture. [b] Yield of the isolated pure products.

Table 6 Thia-Michael addition reactions[a,b]



[a] Reaction conditions: aromatic thiol (1.0 mmol), Michael acceptor (1.5 mmol) in presence of 10 mg $NiFe_2O_4$ NPs under air at 100 °C in water and R_f value in (9 : 1) petroleum ether and ethyl acetate mixture. [b] Yield of the isolated pure products.

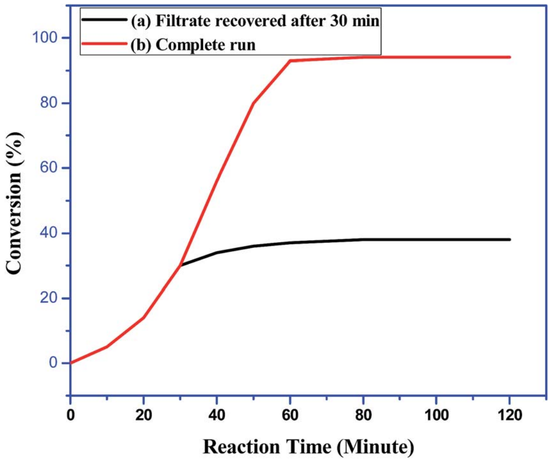


Fig. 4 Results of leaching study by hot filtration test performed with: (a) filtrate removed after 30 min (black line) and (b) complete run (red line) for the synthesis of diethyl 2-(3-oxo-1,3-diphenylpropyl) malonate.

Conclusions

In conclusion, we have demonstrated a simple, efficient, green and clean protocol for the carbon–carbon Michael addition and carbon–heteroatom namely, aza-, oxa-, thia-Michael addition reactions using magnetic nano-$NiFe_2O_4$ as a reusable catalyst. The protocol is general, very clean, mild and the products were obtained in quantitative yields which were purified by column chromatography short silica gel with ease. All the reactions were performed either in neat or water and thus the use of volatile and hazardous solvent have been avoided. The catalyst, $NiFe_2O_4$ NPs were easily separated from the reaction mixture by an external magnet and reused which made the protocol economic and sustainable. Thus, the present protocol fulfils the criteria of green chemistry and we believe that this upshot will find many applications in the field of green synthesis.

Acknowledgements

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16 *General experimental procedure for $NiFe_2O_4$ NPs catalyzed classical Michael addition to alkenes*: representative procedure for the classical Michael addition to 1,3-diphenyl-prop-2-ene-1-one with diethyl malonate. A mixture of 1,3-diphenyl-prop-2-ene-1-one (1 mmol, 208 mg), diethyl malonate (1.2 mmol, 192 mg) and $NiFe_2O_4$ (10 mg) is heated at 100 °C in water–ethanol mixture 2 mL (1 : 1) under open atmosphere for 1 h (TLC-monitored). Then, the reaction mixture was cooled to room temperature and the catalyst was recovered by using an external strong magnetic field. The remaining reaction mixture was evaporated in vacuum to reduce the volume and extracted with ethyl acetate (20 mL), washed with water (5 mL; 3 times) followed by brine solution. Then the extracted solution was dried over anhydrous Na_2SO_4. The crude product was obtained by evaporation of solvent in vacuum which was purified by short column chromatography over silica gel (60–120 mesh) using mixture of petroleum ether and ethyl acetate (90 : 10) as an eluting solvent to afford the pure diethyl 2-(3-oxo-1,3-diphenylpropyl)malonate (Table 2, entry 1; 93%, 342.5 mg) as white solid. R_f value ($R_f = 0.37$) was determined using petroleum ether and ethyl acetate mixture (9 : 1) as an eluting agent. The formation of the product was confirmed by 1H NMR studies. 1H NMR (500 MHz, CDCl3): δ 7.90 (d, $J = 7.0$ Hz, 2H), 7.52 (t, $J = 6.5$ Hz, 1H), 7.43 (t, $J = 6.5$ Hz, 2H), 7.25 (t, $J = 8$ Hz, 4H), 7.15 (t, $J = 6.5$ Hz, 1H), 4.19 (d, $J = 6.5$ Hz, 3H), 3.96 (d, $J = 6.5$ Hz, 2H), 3.83 (d, $J = 9.5$ Hz, 1H), 3.48 (m, 2H), 1.25 (t, $J = 6.5$ Hz, 3H), 1.00 (t, $J = 6.5$ Hz, 3H). The same protocol was followed for all the reaction listed in Table 2.