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A unique approach to magnetization of metal oxides: Nano-Fe₃O₄@TDI@TiO₂ as a highly efficient, magnetically separable and recyclable heterogeneous nanocatalyst

Elham Tabrizian and Ali Amoozadeh*

A highly efficient and magnetically recyclable nanocatalyst has been prepared by covalent grafting of Fe_3O_4 and TiO_2 nanoparticles to 2,4-toluene diisocyanate as an inexpensive and highly reactive linker. The morphology and structure of this novel nanocatalyst was investigated by Fourier transform infrared spectroscopy (FT-IR), field emission scanning electron microscopy (FE-SEM), X-ray diffraction (XRD), thermogravimetric analysis (TGA) and vibrating sample magnetometer (VSM). The catalytic activity of the catalyst was probed for the synthesis of tetrahydrobenzo[*b*]pyran and hexahydroquinoline derivatives at 70 °C under solvent-free conditions with excellent yields and short reaction times. Experimental design was adopted to optimize the reaction conditions by central composite design (CCD). The catalyst can be readily separated by applying an external magnet device and recycled up to 6 times without significant decrease in catalytic activity, which makes it highly beneficial to address the industrial needs and environmental concerns. This is the first study that reports a unique method for magnetization of metal oxides through the usage of TDI as a linker and creating a nanocatalyst by covalent grafting of two metal oxides. Moreover, this method could be extended to link other different metal oxides too as well as the magnetic ones.

1. Introduction

Catalysis is a core area of contemporary science posing major fundamental and conceptual challenges. Nowadays, synthetic chemists focused on the preparation, characterization and use of reusable, easily separable, non-toxic and low-cost catalysts as a major issue of modern chemistry and the use of nanoparticles as heterogeneous catalysts has attracted considerable attention due to their interesting structural features, high levels of activity and enhanced selectivity. Among them, nano metal oxides have been widely applied as efficient catalysts for various synthetic organic transformations due to their high surface area-to-volume ratio and coordination sites which are mainly responsible for their catalytic activity.^{1, 2}

Magnetic Fe₃O₄ nanoparticles are a class of nanostructured metal oxides which are widely applied in various fields, such as magnetic resonance imaging (MRI) contrast agents, magnetically assisted drug delivery and hyperthermia.^{3, 4} Particularly, they have emerged as a useful heterogeneous catalyst in many organic transformations due to low toxicity, high surface area and large surface-to-volume ratio.⁵⁻⁷ Notably, the insoluble and paramagnetic nature of the Fe₃O₄ enable trouble-free separation of this nanocatalyst from the reaction mixture by using an external magnet, which eliminates the necessity of catalyst filtration.

Considering the high catalytic activity of n-TiO₂ and n-Fe₃O₄ and the magnetic properties of n-Fe₃O₄, we have decided to couple these catalysts through a linker in order to synthesize an easy separable nanocatalyst with improved catalytic property, hence we have applied 2,4-toluene diisocyanate (TDI) as a coupling agent which is a kind of bifunctional-group organic chemicals. TDI is readily available, low-cost, and very active due to its highly unsaturated bonds. Furthermore, the reaction between metal oxides and TDI could occur fast, easily and without any catalyst. To the best of our knowledge, there are no literature reports on applying TDI as a linker to join two different metal oxides. So we have decided to estimate the catalytic applicability of the prepared catalyst for synthesizing tetrahydrobenzo[b]pyrans and hexahydroquinolines. It is notable that, this novel strategy opens up avenues for design and engineering a wide variety of new and interesting nanomaterials and nanocatalysts.

2. Result and Discussion

As part of our efforts in exploring heterogeneous catalysts for organic reactions, ¹³⁻¹⁸ we have designed, prepared and characterized nano-

Titanium dioxide nanoparticles (nano-TiO₂) are certainly one of the most interesting metal oxides due to their easy availability, nontoxicity, high activity, reusability, strong oxidizing power and longterm stability.^{8, 9} It has been proved that nano-TiO₂ is an efficient Lewis acid catalyst for the synthesis of wide variety of heterocyclic and organic compounds.^{8, 10-12} Moreover, it is a well-known matter used for photo-electrochemical cell, water or air purification and degrading the organic pollutants.

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 $Fe_3O_4 @TDI @TiO_2$ as a highly efficient, magnetically separable and recyclable nanocatalyst as a novel class of heterogeneous catalysts (Scheme 1).



Scheme 1. Preparation of Fe₃O₄@TDI@TiO₂ nanocatalyst.

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As illustrated in Scheme 1, at the first step, Fe_3O_4 nanoparticles were synthesized by co-precipitation method according to the literature report.¹⁹ Subsequently, n-Fe₃O₄ was treated with excessive TDI in which accessible surface hydroxyls of n-Fe₃O₄ favorably reacted with *para*-isocyanate groups of TDI through the formation of urethane bonds,^{20, 21} leaving the *ortho*-isocyanate groups unreacted due to the different reactivity of the two isocyanate groups together with steric hindrance in TDI molecule.²² Then, n-TiO₂ which was previously synthesized considering the literature report,²³ was added and similarly the surface hydroxyl groups of n-TiO₂ reacted with the unreacted *ortho*-isocyanate groups of n-Fe₃O₄@TDI, however in higher temperature and longer reaction time. It is worth noting that, due to presence of adsorbed water on the surface of almost all nanomaterials, especially oxides, there might be some free primary amino groups present on the surface of the nanocatalyst.

This novel nanocatalyst was characterized via FT-IR, FE-SEM, XRD, TGA, and VSM analyses.

2.1. Characterization of n-Fe $_3O_4@TDI@TiO_2$ FT-IR spectra

Fourier transform infrared spectroscopy (FT-IR) is one of the best techniques to characterize the functionalization of nanoparticles. So, FT-IR spectra of the $n-Fe_3O_4$ and every step of the reaction was analyzed (Fig. 1). In curve a, the adsorption peaks appearing at 578 and 626 cm⁻¹ correspond to the Fe-O bands and broad peaks at 3000–3600 $\rm cm^{-1}$ and 1623 $\rm cm^{-1}$ are respectively attributed to the stretching and bending modes of the O–H of surface hydroxyl groups and physically adsorbed water.²⁴ In curve b, for n-TiO₂, the broad intense band below 1200 cm⁻¹, that is considered as the fingerprint of the TiO_2 , is attributed to Ti-O-Ti vibration and the absorbance at 1623 and 3355 cm⁻¹ are assigned to the surface hydroxyl groups of TiO₂.²⁵ Curve c in Fig. 1 shows the FT-IR spectrum of TDI. The absorption peak at 2243 cm⁻¹ owing to stretching vibration of NCO, which agrees with the literature values,²⁶ is its main peak. The peaks at 1550 cm⁻¹ are reasonably attributed to the phenyl ring of TDI. FT-IR spectrum of TDI-functionalized n-Fe₃O₄ (Fig. 1d), compared with the spectrum of the bare Fe₃O₄ nanoparticle (Fig. 1a), is revealed new peaks at 2262, 1647, 1595, and 1539 cm⁻¹. The peak at 2266 cm⁻¹ can be attributed to the unreacted ortho-isocyanate groups of TDI attached to the n-Fe₃O₄ surface, while the bands at 1647 and 1595 cm⁻¹ can be assigned to the C=O and C-N stretches indicating that the reaction of toluene diisocyanate with n-Fe₃O₄ takes place through the formation of a urethane bond (OCONH)²⁷ and the N-H bond of urethane at 3267 cm⁻¹ may overlapped with broad peaks of surface hydroxyl groups and adsorbed water. Additionally, the peak at 1539 cm⁻¹ is related to the phenyl ring of TDI. These results suggested that TDI was successfully anchored on the surface of Fe₃O₄⁻¹Aanoparticles! In curve e, the fingerprinting IR bands at the range of 500-700 cm⁻¹ shows a bit difference from the Fe-O vibration band at 578 cm⁻¹ (curve a), which is ascribed to Ti-O stretching and Ti-O-Ti bridging stretching modes²⁸ and proves loading of n-TiO₂ onto the surface of n-Fe₃O₄@TDI. Moreover, the isocyanate peak at 2262 cm⁻¹ is disappeared. Thus, the deposition of TiO₂ nanoparticles on n-Fe₃O₄@TDI is certainly achieved.



Figure 1. FT-IR spectra of (a) n-Fe $_3O_4$, (b) n-TiO $_2$, (c) TDI, (d) n-Fe $_3O_4@$ TDI, (e) n-Fe $_3O_4@$ TDI@TiO $_2$.

Thermo gravimetric analysis

One indication of bond formation between the nanoparticles and the TDI can be inferred from thermogravimetric analysis (TGA). Fig. 2 shows thermogravimetric analysis (TGA) curve of n-Fe₃O₄@TDI@TiO₂ in the temperature range 30-800 °C. The thermograph of the n-Fe₃O₄@TDI@TiO₂ depicts two stages decomposition. The first region is below 150 °C which attributed to the loss of trapped water and solvents from the catalyst. The second weight loss (12%) in the region between 150 and 455 °C can be considered as the thermal decomposition of the TDI groups.²⁹ On the basis of these results, the well grafting of TDI is verified.



Figure 2. TGA curve of n-Fe₃O₄@TDI@TiO₂.

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Field emission scanning electron microscopy

Morphological studies of n-Fe₃O₄, n-TiO₂ and n-Fe₃O₄@TDI@TiO₂ were performed using FE-SEM micrographs as shown in Fig. 3. Fe₃O₄ and TiO₂ nanoparticles have an approximate diameter of 20-50 and 20-40 nm with nearly spherical shapes (Fig. 3a and b). After covalent grafting of TDI and n-TiO₂ on the surface of Fe₃O₄ nanoparticles, the resultant nanomaterials still have the morphology of spherical shape with a larger particle size of 80-100 nm (Fig. 3c). These results confirm the presence of the catalyst in nanometer-sized particles.



Figure 3. FE-SEM images of (a) n-Fe₃O₄, (b) n-TiO₂, (c) n-Fe₃O₄@TDI@TiO₂.

X-ray diffraction spectra

The crystalline nature of n-Fe₃O₄@TDI@TiO₂ is demonstrated by XRD and along with X-ray diffraction patterns of Fe₃O₄ and TiO₂ nanoparticles as shown in Fig. 4. In curve a, the peaks at the values of 20 equal to 30.4 (220), 35.7 (311), 43.4 (400), 54.1 (422), 57.1 (511) and 62.9 (440) corresponds to cubic Fe₃O₄ structure which conforms with the JCPD 79-0417 standard and the mean crystalline sizes of Fe₃O₄ nanoparticles are calculated to be 14.5 nm using Debaye-Scherrer's equation, $D=k\lambda/\beta\cos\theta$, where k is a constant (generally considered as 0.94), λ is the wavelength of Cu-Ka (1.54 °A), β is the corrected diffraction line full-width at half-maximum (FWHM), and θ is Bragg's angle.³⁰ As shown in curve b, the typical diffraction signals located at 20 equal to 25.2 (101), 37.3 (103), 37.8 (004), 38.7 (112), 48.2 (200), 54.0 (105), 55.1 (211), 62.8 (204), 68.9 (116), 70.4 (220), 75.1 (215) and 83.1 (224) can be well assigned to the diffraction of TiO₂ nanoparticles with anatase crystalline phase which matched with the standard XRD data of JCPD card Prended 389-4929336d according to Debaye-Scherrer's equation, the average n-TiO₂ diameter for $2\theta = 25.30^{\circ}$ is calculated to be around 22 nm. For the XRD of n-Fe₃O₄@TDI@TiO₂ (Fig. 4c), compared to n-Fe₃O₄ (Fig. 4a), the extra diffraction peaks matched well with those of anatase TiO₂ (Fig. 4b), which approves the modification of magnetic nanoparticles with n-TiO₂. Besides, from the XRD, crystallinity of Fe₃O₄ and TiO₂ nanoparticles are well retained throughout the process.



Figure 4. The X-ray diffraction patterns of the (a) $n-Fe_3O_4$, (b) $n-TiO_2$, (c) $n-TiO_2$, Fe₃O₄@TDI@TiO₂.

Vibrating sample magnetometer

Paramagnetic particles are highly valuable for their magnetic separation; so, the magnetic properties of n-Fe₃O₄ and n- $Fe_3O_4@TDI@TiO_2$ were characterized by a vibrating sample magnetometer (VSM). According to the magnetization curves in Fig. 5, the saturation of the n-Fe₃O₄@TDI@TiO₂ decreases to 30 emu/g from 49 emu/g in the initial Fe₃O₄ sample due to the existence of nonmagnetic materials on the surface of n-Fe₃O₄, which is still sufficient for quickly magnetic separation with a conventional magnet. Nonetheless, the reversibility in hysteresis loop confirms that no aggregation occurs to the nanoparticles in the magnetic fields. Moreover, according to curve c, the recycled catalyst after 6 runs showed very slight decrease (28 emu/g) in the magnetization value which could be still easily separated from solution under an external magnetic field.





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2.2. Evaluation of the catalytic activity of n-Fe $_3O_4$ @TDI@TiO $_2$

Tetrahydrobenzo[*b*]pyrans, as an important class of oxygencontaining heterocycles, are of considerable interest because of their useful pharmacological and biological properties. Furthermore, they are versatile synthons that can be easily converted into pyridine compounds as pharmacologically important calcium antagonists.^{31, 32} Due to the versatile utilization of the pyran derivatives in the field of organic synthesis as well as in medicinal chemistry, we have investigated catalytic activity of n-Fe₃O₄@TDI@TiO₂ as a heterogeneous nanocatalyst for their synthesize (Scheme 2).



Scheme 2. Synthesis of tetrahydrobenzo[b]pyrans using n-Fe₃O₄@TDI@TiO₂ a: nanocatalyst.

For this purpose, the reaction of dimedone, benzaldehyde and malononitrile as a model reaction was probed to establish the feasibility of the strategy and optimize the reaction conditions. In order to find the optimal conditions, the central composite design (CCD), one of the most applicable types of response surface model (RSM), was applied which offers benefits of attaining the same amount of information while keeping the number of experimental conditions minimal, without losing precision. It has been accepted as an effective optimization method in attainment to improved responses *via* a fitted quadratic model which can be expressed by following equation:

$$Y = \beta_0 + \sum_{i=1}^4 \beta_i \, X_i + \sum_{i=1}^4 \sum_{j=1}^4 \beta_{ij} \, X_i X_j + \sum_{i=1}^4 \beta_{ii} \, {X_i}^2$$

In which Y is response, X_i and X_j are independent variables, β_0 is the constant model, β_i , β_{ii} and β_{ij} are coefficients for the linear, quadratic and interaction effects, respectively.

First, preliminary experiments were carried out to investigate the appropriate parameters and to determine the experimental domain. According to these experiments, the effects of catalyst amount (X_1) , temperature (X_2) , and reaction time (X_3) were performed on reaction yield as response. A five-level CCD of three independent variables with their corresponding values are shown in Table 1. Actual values of each factor are represented in coded pattern.

| Indonondont | | phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile. Levels | | | | | | |
|--|-------------|---|-------------|----|---------------|--------------|----------|----------------|
| variables | Low (-1. | est 68) | Low (-1) | Ce | entral (0) | High (+1) | Hi (+ | ghest 1.68) |
| X ₁ : Catalyst amou (mg) | unt | 15 | | 20 | 25 | | 30 | 35 |
| X ₂ : Temperature | (°C) | 50 | | 60 | 70 | | 80 | 90 |
| X₃: Time (sec) | | 60 | | 90 | 120 | | 150 | 180 |

Based on CCD method, total number of experiments was found to be 20 which consisted of eight full factorial points, six axial points and six central points. The design layout and response, values, are shown in Table 2.

 Table 2. Conditions of predicted experiments in CCD for three effective factors in the synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4Hchromene-3-carbonitrile.

| Run | X1 | X ₂ | X ₂ | Vield (%) |
|-----|-------|----------------|----------------|-----------|
| 1 | 0 | 0 | 0 | 94.45 |
| 2 | 0 | +1.68 | 0 | 02 20 |
| 2 | 1 | +1.08 | 11 | 95.20 |
| 5 | +1 | -1 | +1 | 02.01 |
| 4 | 0 | 0 | 0 | 92.00 |
| 5 | -1 | -1 | -1 | 58.05 |
| 6 | -1 | +1 | -1 | 73.18 |
| 7 | +1 | +1 | -1 | 82.45 |
| 8 | 0 | 0 | 0 | 94.00 |
| 9 | 0 | 0 | 0 | 92.56 |
| 10 | 0 | 0 | 0 | 92.88 |
| 11 | 0 | 0 | +1.68 | 88.00 |
| 12 | -1.68 | 0 | 0 | 69.28 |
| 13 | -1 | -1 | +1 | 67.35 |
| 14 | +1 | -1 | -1 | 64.90 |
| 15 | 0 | -1.68 | 0 | 65.55 |
| 16 | +1.68 | 0 | 0 | 90.60 |
| 17 | -1 | +1 | +1 | 82.10 |
| 18 | 0 | 0 | 0 | 93.96 |
| 19 | +1 | +1 | +1 | 95.20 |
| 20 | 0 | 0 | -1.68 | 63.55 |

The analysis of variance (ANOVA) performed on the model can give valuable information on the significance of fitted model and its terms. From the ANOVA, as shown in Table 3, p-values of model and lack of fit are lower and higher than 0.05, respectively which means fitted model is significant in confidence level of 95%. Additionally, the results imply that all the independent variables (X₁, X₂ and X₃) and their quadratic terms (X₁², X₂² and X₃²) significantly affect the response value (yield), and a significant interaction between catalyst amount (X₁) and time (X₃) is apparent (P<0.05). Also, the amounts of R-squared and adj R-squared are above 0.9 and close to each other, indicates fitted model has high accuracy and reliability in prediction of the reaction yield. In other words, there is a good agreement between experimental and the predicted responses which confirms the suitability of the following model.

| Table 3. Analysis of variance for the response surface quadratic model for yield. | | | | | | |
|---|---|----|--------|--------|---------------------|--|
| Sourco | Sum of | qt | Mean | F | p-value | |
| Source | Squares | ui | Square | Value | Prob > F | |
| Model | 3097.89 | 9 | 344.21 | 143.21 | < 0.0001 | |
| X ₁ : Catalyst amount | 501.23 | 1 | 501.23 | 208.54 | < 0.0001 | |
| X ₂ : Temperature | 793.84 | 1 | 793.84 | 330.29 | < 0.0001 | |
| X₃: Time | 622.46 | 1 | 622.46 | 258.98 | < 0.0001 | |
| X_1X_2 | 0.57 | 1 | 0.57 | 0.24 | 0.6361 | |
| X_1X_3 | 26.79 | 1 | 26.79 | 11.15 | 0.0075 | |
| X_2X_3 | 7.49 | 1 | 7.49 | 3.12 | 0.1080 | |
| X_1^2 | 364.26 | 1 | 364.26 | 151.55 | < 0.0001 | |
| X_2^2 | 393.78 | 1 | 393.78 | 163.84 | < 0.0001 | |
| X ₃ ² | 608.89 | 1 | 608.89 | 253.34 | < 0.0001 | |
| Residual | 24.03 | 10 | 2.40 | | | |
| Lack of Fit | 19.37 | 5 | 3.87 | 4.16 | 0.0720 | |
| Pure Error | 4.66 | 5 | 0.93 | | | |
| Cor Total | 3121.93 | 19 | | | | |
| R ² = 0.99 | R ² = 0.99 Adj-R ² = 0.98 | | | | ² = 0.94 | |

Based on the ANOVA results, the following equation was obtained:

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$$Y$$
 (Yield) = $-502.97 + 10.18X_1 + 8.60X_2 + 1.88X_2 - 1000$

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 $\begin{array}{l} Y \mbox{ (Yield)} = -502.97 + 10.18 X_1 + 8.60 X_2 + 1.88 X_3 - 5.35 \times 10^{-3} X_1 X_2 \\ + \mbox{ } 0.01 X_1 X_3 - 3.22 \times 10^{-3} X_2 X_3 - 0.2 X_1^2 - 0.05 X_2^2 \\ - \mbox{ } 7.22 \times 10^{-3} X_3^2 \end{array}$

The coefficients of the equation show the effect of the parameters. The more the value is, the more the effect is. So, it can be realized from response equation that the X_1 has the most linear effect on the product yield, therefore the amount of catalyst can be considered as the main factor in progressing the reaction.

In order to investigate the main interaction effects between two parameters on the yield of reaction, three-dimensional profiles of yield versus a pair of parameters were applied (Fig. 6). According to their p-values, interaction of X_1X_3 is significant; it means that simultaneous increment of the catalyst amount and time cause to — increase the product yield until 28 mg of the catalyst within 2 min.



Figure 6. Three-dimensional response surfaces for the effect of factors on the reaction yield.

Based on the 30 experimental data, with the aid of desirability function by using Design-Expert 7.0.0., the model predicted the optimum yield for this reaction could reach 95.52%, with the optimal process conditions of 28 mg catalyst, 70 °C reaction temperature within 2 min (Fig. 7). In order to verify the adequacy of the model, three parallel experiments were conducted, under the above conditions and negligible difference between the average yields and the prediction values of software was observed which meant that the predicted and experimental data had a good agreement.



At the next step, the scope and generality of this protocol for various aromatic aldehydes and cyclic 1,3-diketone compounds was investigate under the optimized conditions (Table 4).

| Table 4. Synthesis of tetral | nydrobenzo[<i>b</i>]pyran de | erivatives by n-Fe ₂ O | ₄@TDI@TiO ₂ |
|------------------------------|--------------------------------|-----------------------------------|------------------------|

| F. | ٨٣ | D ¹ -D ² | Time (min) | Yield ^ь (%) | Melting point (°C) | | |
|-----------|---|--------------------------------|---------------|---------------------------|--------------------|-----------------------|--|
| Entry | Ar | к-=к- | | | Found | Reported | |
| 1 | -C6H₅ | Н | 2 | 94 | 212-214 | 213-215 ³³ | |
| 2 | $4-H_3C-C_6H_4$ | н | 3 | 90 | 232-234 | 234-236 ³⁴ | |
| 3 | $4-H_3CO-C_6H_4$ | н | 3 | 91 | 190-191 | 190-192 ³³ | |
| 4 | $4-HO-C_6H_4$ | н | 4 | 85 | 233-234 | 234-236 ³³ | |
| 5 | $2-O_2N-C_6H_4$ | н | 3 | 94 | 195-197 | 196-198 ³³ | |
| 6 | $3-O_2N-C_6H_4$ | н | 2 | 95 | 200-201 | 201-202 ³³ | |
| 7 | $4-O_2N-C_6H_4$ | н | 1 | 97 | 234-235 | 235-237 ³⁴ | |
| 8 | 2-CI-C ₆ H ₄ | н | 2 | 94 | 212-213 | 212-214 ³³ | |
| 9 | 4-CI-C ₆ H ₄ | н | 1 | 97 | 226-228 | 225-227 ³⁴ | |
| 10 | $4-Br-C_6H_4$ | н | 1 | 88 | 229-232 | 235-238 ³¹ | |
| 11 | 2-Furfural | н | 4 | 94 | 202-204 | 199-200 ³³ | |
| 12 | $4-(CH_3)_2N-C_6H_4$ | н | 2 | 91 | 171-173 | 171-174 ³¹ | |
| 13 | C ₆ H₅-CH=CH- | н | 4 | 80 | 192-193 | 195-198 ³¹ | |
| 14 | -C6H5 | CH₃ | 2 | 95 | 228-230 | 229-230 ³² | |
| 15 | $4-H_3C-C_6H_4$ | CH₃ | 3 | 91 | 217-219 | 215-217 ³⁵ | |
| 16 | $4-H_3CO-C_6H_4$ | CH₃ | 2 | 90 | 199-200 | 196-198 ³⁵ | |
| 17 | $4-HO-C_6H_4$ | CH₃ | 3 | 83 | 206-207 | 205-206 ³³ | |
| 18 | $2-O_2N-C_6H_4$ | CH₃ | 3 | 91 | 224-225 | 224-226 ³³ | |
| 19 | $3-O_2N-C_6H_4$ | CH₃ | 2 | 95 | 204-206 | 211-212 ³³ | |
| 20 | $4-O_2N-C_6H_4$ | CH₃ | 1 | 98 | 174-176 | 174-176 ³⁵ | |
| 21 | 2-CI-C ₆ H ₄ | CH₃ | 2 | 94 | 211-213 | 212-213 ³⁵ | |
| 22 | $4-CI-C_6H_4$ | CH₃ | 1 | 97 | 211-213 | 208-210 ³² | |
| 23 | 4-Br-C ₆ H ₄ | CH₃ | 1 | 89 | 206-208 | 207-208 ³² | |
| 24 | $4-F-C_6H_4$ | CH₃ | 2 | 92 | 221-223 | - | |
| 25 | 4-(CH ₃) ₂ N-C ₆ H ₄ | CH₃ | 1 | 95 | 210-212 | 206-208 ³¹ | |
| 26 | 2-Naphthyl | CH₃ | 2 | 89 | 229-231 | - | |
| 27 | 2-Furfural | CH₃ | 3 | 93 | 205-206 | 201-203 ³³ | |
| 28 | C ₆ H ₅ -CH=CH- | CH₃ | 4 | 81 | 190-192 | 185-188 ³¹ | |

^a Reaction conditions: 1 (1 mmol), 2 (1 mmol), 3 (1 mmol), n-Fe₃O₄@TDI@TiO₂ (0.028 g) under solvent-free condition at 70 °C.
^b Isolated yield.

Interestingly, a variety of 1,3-cyclic diketones and aryl aldehydes bearing electron-withdrawing or electron-donating substituents (ortho-, meta-, and para-substituted) participated well in this reaction and gave the product in good to excellent yield (80-98%) within 1-4 min. Moreover, heteroaromatic aldehyde could also successfully convert to its corresponding tetrahydrobenzo[*b*]pyran product with excellent yield (Table 4, entries 11 and 24). The formation and purity of products was confirmed by their melting point determination which were in good accordance with the literature values and the structures of some of the products were well characterized by using FT-IR, ¹H NMR and ¹³C NMR spectral data.

The plausible mechanism for the formation of tetrahydrobenzo[b]pyrans is outlined in Scheme 3 which is consist of three major stages: Knoevenagel condensation, Michael addition and finally intramolecular ring closure.³⁶ Due to Lewis acidity of the Fe₃O₄ and TiO₂ nanoparticles, n-Fe₃O₄@TDI@TiO₂ acts as a catalyst and activates methylene compound (I) and aldehyde (II) to facilitate

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the formation of the Knoevenagel condensation product (III) _____ followed by a dehydration step (IV). Then, 1,3-cyclic dicarbonyl _____ compound (V) converts to its enole form after tautomerisation (VI) _____ and attack the electrophilic center of (IV) to form a carbon–carbon bond *via* a Michael addition (VII) followed by tautomerism and intramolecular *O*-cyclization (VIII). It is noteworthy to mention that, during ring closure step, the catalyst plays the critical role in which it can minimize the 1,2 dipolar repulsion between the geminal nitrile groups and activates one of the nitriles by polarization (through coordination). The latter is then tautomerization and proton transfer which leads to the desired product (VIIII).



Scheme 3. Possible mechanism for the synthesis of tetrahydrobenzo[b]pyrans in the presence of $n-Fe_3O_4$ @TDI@TiO_2 as a nanocatalyst.

Encouraged by these results and in order to generalize the catalytic efficiency of $n-Fe_3O_4$ @TDI@TiO₂, our study was followed by the synthesis of hexahydroquinolines *via* a four-component cyclocondensation reaction using cyclic 1,3-diketones, benzaldehydes, malononitrile and ammonium acetate under the optimized condition reaction of tetrahydrobenzo[*b*]pyrans (Scheme 4).



Scheme 4. Synthesis of hexahydroquinolines using n-Fe₃O₄@TDI@TiO₂ as nanocatalyst.

| Table 5. Synthesis of hexahydroquinoline derivatives by n-Fe ₃ O ₄ @TDI@TiO _{&triclo} Opline | | | | | | | |
|---|------------------------------------|-------|-------|---------------------------------|---------|-----------------------|---|
| · | A | p1 p2 | Time | Yield DOI: 10 Meiting (pointo(3 | | | |
| | Ar | K-=K- | (min) | (%) | Found | Reported | |
| 1 | -C6H₅ | Н | 20 | 90 | 257-258 | 257 ³⁷ | • |
| 2 | $4-H_3C-C_6H_4$ | н | 22 | 88 | 260-261 | 258 ³⁷ | |
| 3 | $4-H_3CO-C_6H_4$ | Н | 25 | 85 | 277-279 | 278 ³⁷ | |
| 4 | $2-O_2N-C_6H_4$ | н | 30 | 87 | 228-230 | - | |
| 5 | $3-O_2N-C_6H_4$ | Н | 15 | 90 | 240-242 | 243 ³⁷ | |
| 6 | $4-O_2N-C_6H_4$ | Н | 15 | 90 | 259-260 | 260 ³⁷ | |
| 7 | 2-CI-C ₆ H ₄ | Н | 18 | 91 | 286-288 | 286 ³⁷ | |
| 8 | 4-CI-C ₆ H ₄ | Н | 20 | 93 | 287-289 | 289 ³⁷ | |
| 9 | $4-Br-C_6H_4$ | Н | 19 | 92 | 250-252 | - | |
| 10 | $4-F-C_6H_4$ | н | 18 | 95 | 286-287 | 286 ³⁷ | |
| 11 | -C6H5 | CH₃ | 20 | 92 | 278-279 | 275-277 ³⁸ | |
| 12 | $4-H_3C-C_6H_4$ | CH₃ | 25 | 89 | 290-293 | 294-295 ³⁸ | |
| 13 | $4-H_3CO-C_6H_4$ | CH₃ | 27 | 88 | 289-291 | 289-293 ³⁸ | |
| 14 | $2-O_2N-C_6H_4$ | CH₃ | 20 | 90 | 231-234 | - | |
| 15 | $3-O_2N-C_6H_4$ | CH₃ | 15 | 93 | 284-285 | 282-283 ³⁹ | |
| 16 | $4-O_2N-C_6H_4$ | CH₃ | 17 | 89 | 293-295 | 290-292 ³⁹ | |
| 17 | 2-CI-C ₆ H ₄ | CH₃ | 14 | 91 | 271-273 | 273-276 ³⁸ | |
| 18 | 4-CI-C ₆ H ₄ | CH₃ | 17 | 90 | 291-293 | 290-291 ³⁹ | |
| 19 | $4-Br-C_6H_4$ | CH₃ | 18 | 90 | 295-298 | 295-296 ³⁹ | |
| 20 | $4-F-C_6H_4$ | CH₃ | 15 | 94 | 297-298 | 299-300 ³⁹ | |
| 21 | $4-(CH_3)_2N-C_6H_4$ | CH₃ | 35 | 85 | >300 | >300 ³⁹ | |
| 22 | 2-Naphthyl | CH₃ | 40 | 82 | 260-263 | - | |

 a Reaction conditions: 1 (1 mmol), 2 (1 mmol), 3 (1 mmol), 6 (2.5 mmol), n-Fe_3O_4@TDI@TiO_2 (0.028 g) under solvent-free condition at 70 °C. b Isolated yield.

As indicated in Table 5, the reaction works easily for a vast variety of aromatic aldehydes with both electron-donating and electron-withdrawing groups and different cyclic di-ketones, giving corresponding hexahydroquinoline derivatives in good to excellent yields which are in good accordance with melting points of literature values. Moreover, the structures of some of the products were well characterized by using FT-IR, ¹H NMR and ¹³C NMR spectral data.

The suggested mechanism for the synthesis of hexahydroquinolines is shown in Scheme 5. This mechanism is similar to that of benzo[*b*]pyrans, but due to presence of ammonium acetate, 1,3-cyclic dicarbonyl compound (**V**) condenses with NH_4OAc (**VI**) to give (**VII**) followed by removal of an acetic acid and in the intramolecular ring closure step, nitrogen atom acts as a nucleophile (**VIII**) and intramolecular *N*-cyclization occurs (**IX**) which leads to final product (**X**).



 $\label{eq:Scheme 5.} Suggested mechanism for the synthesis of hexahydroquinolines in the presence of n-Fe_3O_4@TDI@TiO_2 as a nanocatalyst.$

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In order to compare the efficiency of the prepared Lewis acid nanocatalyst with other reported Lewis acid nanocatalysts as well as to exhibit the merit of the present work, our results are compared with some other previously reported studies in the Table 6.

Table 6. Comparison of n-Fe₃O₄@TDI@TiO₂ with some of the reported catalysts in the synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile.

| Entry | Catalyst | Reaction condition | Time (min) | Yield (%) | Ref |
|-------|--|-----------------------------|---------------|--------------|-----|
| 1 | n-Pd | CH₃CN/reflux | 300 | 87 | [35 |
| 2 | n-ZnO | EtOH:H₂O/r.t. | 210 | 86 | [36 |
| 3 | n-TiO ₂ | Solvent-free/70 °C | 35 | 92 | [40 |
| 4 | n-SiO ₂ | EtOH/r.t. | 25 | 94 | [41 |
| 5 | n-Fe ₃ O ₄ @SiO ₂ @TiO ₂ | Solvent-free/95 °C | 20 | 93 | [32 |
| 6 | n-Fe ₃ O ₄ | Solvent-free/100 °C | 15 | 81 | [32 |
| 7 | n-PbO | Grinding/r.t. | 15 | 83 | [42 |
| 8 | n-CoFe ₂ O ₄ | EtOH:H ₂ O/60 °C | 7 | 93 | [31 |
| 9 | n-Fe ₃ O ₄ @TDI@TiO ₂ | Solvent-free/70 °C | 2 | 95 | Thi |
| 5 | | | - | 20 | wor |

It is evident from the Table 5 that, $n-Fe_3O_4$ @TDI@TiO₂ is highly efficient in minimizing the reaction time and even in terms of product yield, catalyst amount, elimination of solvent, easy separation and recovery of the catalyst. These advantages can be attributed to the highly activity due to nano porosity and high surface area of the catalyst.

Recycling of the catalyst

From the industrial and large scale operations points of view, reusability is the principal advantage for an efficient heterogeneous catalyst. Hence, the reusability of the catalyst was scanned. Findings revealed the same catalytic activity for the six times reused catalyst as the fresh one, without any loss of the activity which means that the catalyst structure is preserved (Fig. 8).



 $\label{eq:Figure 8.} Fe (a) $ Fe_3O_4 (@TDI (@TiO_2 for the synthesis of benzo[b] pyrans, Reaction conditions: dimedone (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol) and n-Fe_3O_4 (@TDI (@TiO_2 (28 mg); reaction time: 2 min at 70 °C under solvent free condition.$

The identity of the recovered catalyst was checked by FE-SEM which suggested that the nature of the catalyst remains intact and there was no change in the morphology during the reaction and recycling stages as compared to the fresh catalyst (Fig .9).



Figure 9. FE-SEM images of n-Fe₃O₄@TDI@TiO₂ before use (a) and after reused six times (b).

] 3. Experimental

Materials and instruments

All chemicals were used without any further purification and purchased from the Merck and Aldrich chemical companies. Toluene diisocyanate (TDI) was in industrial grade with 80:20 mixture of 2,4 and 2,6 isomers and it was used as received. Solvents were purified by conventional methods. The purity of products was checked by thin Tayer chromatography (TLC) on glass plates coated with silica gel 60

F254 using n-hexane/ethyl acetate mixture as mobile phase. Melting points were recorded on THERMO SCIENTIFIC 9100 apparatus. Fourier transform infrared spectroscopy (FT-IR) were recorded on a Shimadzu 8400 spectrometer in the range of 400-4000 cm⁻¹ using KBr pressed powder discs. Thermogravimetric analyses (TGA) were conducted using a Du Pont 2000 thermal analysis apparatus heated from 25°C to 800 °C at ramp 5°C/min under air atmosphere. Field emission scanning electron microscope (FE-SEM) images were acquired with a Philips XL30 field emission scanning electron microscope (Royal Philips Electronics, Amsterdam, The Netherlands) instrument operating at 25 kV. Particles were mounted on a double sided adhesive carbon disk and sputter-coated with a thin layer of gold to prevent sample charging problems. Wide-angle X-ray diffraction (XRD) measurements were performed at room temperature on a Siemens D5000 (Siemens AG, Munich, Germany) using Cu-Ka radiation of wavelength 1.54 °A. The magnetite measurement was carried out in a vibrating sample magnetometer (VSM) (4 inch, Daghigh Meghnatis Kashan Co., Kashan, Iran) at room temperature. ¹H and ¹³CNMR spectra were recorded on Bruker Advance Spectrometer 300 & 400 MHz and 75 & 100 MHz respectively, in CDCl₃-d and DMSO-d⁶ with tetramethylsilane (TMS) as the internal reference.

Preparation of the magnetic Fe₃O₄ nanoparticles

Magnetic Fe₃O₄ nanoparticles were prepared by co-precipitation of Fe²⁺ and Fe³⁺ ions with NH₄OH following the reported procedure.¹⁹ FeCl₃·6H₂O (5.838 g, 0.0216 mol) and FeCl₂·4H₂O (2.147 g, 0.0108 mol) were added to 100 mL deionized water at 80–85 °C under N₂ atmosphere and vigorous stirring. Next, 10 mL of 25% aqueous ammonia was quickly added into the reaction mixture in one portion which resulted in immediate precipitation of MNPs. The reaction continued for another 30 min and was cooled to room temperature. The resulted black precipitate was separated by applying an external magnet, washed five times with distilled water and dried in vacuum at room temperature for 48 hr.

Functionalization of Fe_3O_4 nanoparticle with TDI (n-Fe₃O₄@TDI)

A mixture of 1.0 g Fe_3O_4 nanoparticle and 1.40 g TDI was dispersed in 50 mL dried toluene and placed in an ultrasonic bath for 10-15 min.

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Then the reaction mixture was maintained at the temperature of 95 $^{\circ}$ C by a thermostat and stirred for 20 h under the atmosphere of nitrogen. The powder product was magnetically separated and carefully washed with dry toluene to remove the unreacted and physical absorbed TDI. The product, was dried in vacuum at 100 $^{\circ}$ C for 4 h.

Preparation of TiO₂ nanoparticles

The nano-TiO₂ was synthesized by hydrothermal method according to the previously reported procedure.²³ Briefly, NH₃.H₂O was added to TiCl₄ solution until the pH value become 1.8. After stirring for 2 h at 70 °C, the final pH of the solution was adjusted to 6. The resulting suspension was aged at ambient temperature for 24 h. The final product was filtered, washed with NH₄Ac-HOAc until no Cl⁻ was detected. Then, the precipitate was separated using a centrifuge and was washed with ethanol, dried in a vacuum. After 2 h treatment at 650 °C, TiO₂ nanoparticles were obtained.

Preparation of the $n-Fe_3O_4@TDI@TiO_2$

1.0 g Fe₃O₄@TDI nanoparticles were dispersed in 100 mL dried toluene. Subsequently, 0.3 g TiO₂ nanoparticles were added into the dispersion and heated at 110 °C under constant stirring for 24 h. The product was magnetically separated, washed with acetone and then dried at 100 °C for 4 h.

General procedure for the synthesis of tetrahydrobenzo[b]pyran derivatives

In a typical experiment, 1,3-cyclic di-ketone (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol) and n-Fe₃O₄@TDI@TiO₂ (28 mg) were taken in a 25 mL round bottomed flask under solvent free condition and stirred at 70 °C for an appropriate time. Upon completion of reaction (monitored by TLC), the catalyst was separated by exposure to an external magnet (within 10 s). The reaction mixture was decanted an eluted with hot ethanol (5 mL). The title compounds were obtained in their crystalline forms by recrystallization of ethanol solution.

General procedure for the synthesis of hexahydroquinoline derivatives

A mixture of 1,3-cyclic di-ketone (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol), ammonium acetate (2.5 mmol) and n-Fe₃O₄@TDI@TiO₂ (28 mg) were taken in a 25 mL round bottomed flask under solvent free condition and stirred at 70 °C for an appropriate time. Upon completion of reaction (monitored by TLC), the catalyst was separated by exposure to an external magnet (within 10 s). The reaction mixture was decanted an eluted with hot ethanol (5 mL). The title compounds were obtained in their crystalline forms by recrystallization of ethanol solution.

General procedure for recycling of n-Fe₃O₄@TDI@TiO₂

In order to probe the recoverability and recyclability of catalyst, the condensation of dimedone (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol) under the optimized conditions was chosen as model reaction. Upon completion of the reaction, the catalyst was separated *via* an external magnet, washed thoroughly with acetone (2 × 5 mL) and ethanol (2 × 5 mL), dried at 70 °C for 2 h to be used for subsequent reactions.

Conclusions

DOI: 10.1039/C6CY00316H Core shell and composites are routine approaches for magnetization of metal oxides. In our unique and powerful strategy, a novel method for magnetization of metal oxides is presented through the usage of TDI as linker due to the regioselectivity of two different isocyanate groups. Moreover, this method could be extended to link other different metal oxides too as well as the magnetic ones. So an exclusive route for the synthesis of a heterogeneous nanocatalyst is reported here through the action of the organic linker, toluene diisocyanate, in which two metal oxide nanoparticles are linked to together. Nano-Fe₃O₄@TDI@TiO₂ was successfully synthesized and applied for synthesize of tetrahydrobenzo[b]pyrans and hexahydroquinolines by a one-pot multicomponent reactions strategy under solvent-free conditions. Short reaction times, high yields of products, solvent-free with mild reaction conditions, easy magnetically separability and reusability of the catalyst are the main superiorities of this unique nanocatalyst.

Acknowledgements

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Graphical abstract



 $\label{eq:nano-Fe_3O_4} Nano-Fe_3O_4@TDI@TiO_2 \mbox{ as a novel heterogeneous nanocatalyst is synthesized by covalent linkage of $n-Fe_3O_4$ and $n-TiO_2$ through the TDI.}$