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Magnetically retrievable nano crystalline $CuFe_2O_4$ catalyzed multi-component reaction: a facile and efficient synthesis of functionalized dihydropyrano[2,3-*c*]pyrazole, pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives in aqueous media†

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$CuFe_2O_4$ magnetic nanoparticles were synthesized and recognized as an efficient catalyst for the one-pot synthesis of dihydropyrano[2,3-*c*]pyrazole, pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives at mild conditions and in excellent yields. The four component reaction (4CRs) of a wide variety of substituted hydrazine derivatives, ethyl acetoacetate, dialkyl acetylenedicarboxylates and alkyl nitrile derivatives (malononitrile and ethyl cyanoacetate) gave the targeted dihydropyrano[2,3-*c*]pyrazoles. When two equivalents of dialkyl acetylenedicarboxylates were introduced replacing ethyl acetoacetate, a new four-component reaction took place providing another type of dihydropyrano[2,3-*c*]pyrazole derivatives. An efficient and practical route to pyrano[3,2-*c*]coumarin and 4*H*-chromene framework has also been developed by one-pot, three-component reaction (3CRs) of 4-hydroxycoumarin/dimedone/cyclohexane-1,3-dione, dialkyl acetylenedicarboxylates and alkyl nitriles. $CuFe_2O_4$ magnetic nanoparticles were prepared by a simple and effective citric acid complex method and characterized by using XRD, FT-IR, EDX and TEM image. The catalyst was recycled for six cycles with almost unaltered catalytic activity. All reactions were easily performed and proceeded with high efficiency under very simple and mild conditions and gave excellent yields avoiding time-consuming, costly syntheses, and tedious workup and purification of products.

Introduction

Dihydropyrano[2,3-*c*]pyrazoles are one of the most well-known heterocyclic scaffold, since a large number of these molecular frameworks show interesting biological activities and are often part of various pharmaceutical compositions.[1] Pyrano-[3,2-*c*]coumarins, the fused tricyclic derivatives of coumarin are also known for their medicinal properties. These derivatives show antihyperglycemic and antidyslipidemic,[2] cytotoxic,[3] molluscicidal,[4] anti-inflammatory,[5] and antifungal activities.[6] These compounds also exhibit a wide spectrum of biological activities,[7] including anticancer,[8] antimalarial[9] and are also widely employed as cosmetics, pigments[10] and potential biodegradable agrochemicals.[11] Furthermore pyrano-[3,2-*c*]coumarin and 4*H*-chromene derivatives are components of numerous natural products like calanolides, calanone, calophyllolides *etc.*[12] 4*H*-Chromene derivatives are also considered as a venerable pharmacophore and has a wide range of biological applications (compounds A–C, Fig. 1) *e.g.* inhibitors of EAAT1 (excitatory amino acid transporters), anticancer agent and Bcl-2 inhibitor, respectively.[13]

To the best of our knowledge, only a few references exist concerning their synthesis.[14] Although these reported reactions have developed some useful synthetic procedures, still several limitations have remained. For example, most of the procedures involve low yields, or use of organic solvents, or non-recoverable organo catalysts. Thus, a simple, efficient, and green method to synthesize these highly important heterocycles would be attractive.

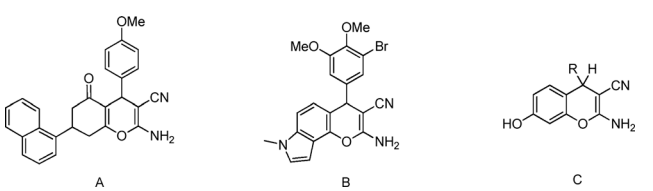

Fig. 1 Biologically active 4*H*-chromene derivatives.

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† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra of all the compounds. CCDC 959948, 959885, and 968630. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cy00901g

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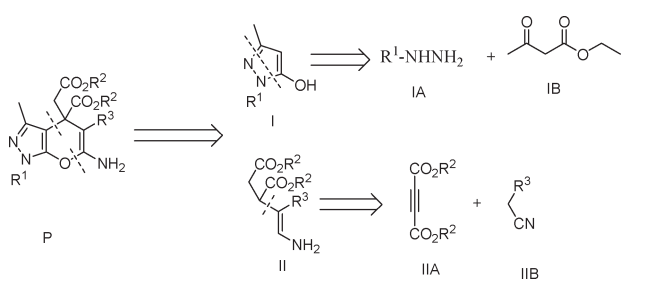
Catalytic processes in aqueous medium are important in many areas of the fine and specialty chemical industries, and the use of solid catalysts means easier catalyst separation and recovery, hence facilitating their reuse. It is widely accepted that a smaller catalyst particle means a higher activity.[15] As a result, both the activity and the stability of a solid catalyst suspended in a liquid media can benefit greatly with the use of these small particles. Nano-catalysts mimic homogeneous (high surface area, easily accessible) as well as heterogeneous (stable, easy to handle) catalyst systems. The main difficulty, however, is that such small particles are almost impossible to separate by conventional means, which can lead to the blocking of valves by the catalyst. To overcome this issue, the use of magnetic nanoparticles has emerged as a viable solution; their insoluble and paramagnetic nature enables easy and efficient separation of the catalysts from the reaction mixture by using an external magnet. Other exciting properties of these magnetic materials include their highly active and specific centers; these features serve to encourage this relatively novel but vastly expanding field. They offer a promising option that can meet the requirements of high accessibility with improved reusability. One of the most attractive features of magnetically separable nanoparticles (MSNPs) is their separation properties. Most heterogeneous systems require a filtration or centrifugation step and/or a tedious workup of the final reaction mixture to recover the catalyst. However, magnetically supported catalysts can be recovered with an external magnet due to their paramagnetic character. Magnetically recoverable materials have been applied in a wide range of catalytic reactions, including oxidations, hydrogenations, photocatalysis, and C–C bond formation, as well as in novel applications in asymmetric synthesis, hydration, Knoevenagel condensations, and CO_2 cycloaddition reactions.[16–18] There has been an increasing trend toward the use of MSNPs in increasingly efficient green chemical synthesis.

Multicomponent reactions[19] (MCRs) have emerged as a highly valuable tools for the rapid generation of molecular complexity and diversity with predefined functionality in chemical biology and drug discovery, due to its straightforward reaction design, convergent, and atom efficient nature resulting in substantial minimization of waste, labour, time, and cost.[20,21] In continuation of our research program dedicated to the design and synthesis of novel heterocyclic systems,[22] we have started our investigation with the objective of developing a clean, efficient and straightforward methodology for the synthesis of dihydropyrano[2,3-*c*]pyrazole, pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives. In addition to the previous report for the synthesis of functionalized dihydropyrano[2,3-*c*]pyrazole and 4*H*-chromene derivatives,[23] in this paper, we report our design of such a direct synthesis of dihydropyrano[2,3-*c*]pyrazole, pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives. The syntheses of these heterocyclic systems have been performed by assembling the basic building blocks using nano $CuFe_2O_4$ as the efficient magnetically recoverable catalyst.

Results and discussion

Due to very wide spectrum of biological potency, our efforts were directed in exploring a more simple and efficient method for the synthesis of substituted dihydropyrano[2,3-*c*]pyrazole, pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives. To introduce more structural diversity and to develop a more efficient protocol, we have tried to synthesize dihydropyrano[2,3-*c*]pyrazole core by advocating a four component coupling reaction of substituted hydrazines (IA), ethyl acetoacetate (IB), dialkyl acetylenedicarboxylates (IIA) and malononitrile or ethyl cyanoacetate (IIB, Scheme 1).

In order to find the best reaction conditions for the synthesis of dihydropyrano[2,3-*c*]pyrazole, pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives, our preliminary investigations focused on the search for a suitable catalyst. At the outset of our studies, we tested representative Brønsted and Lewis acid catalysts ZnO, nano Al_2O_3, $InCl_3$, $H_6P_2W_{18}O_{62}$, $18H_2O$, *p*-toluenesulphonic acid, CF_3CO_2H, SiO_2, Fe_2O_3 and CuO for the four-component reaction of phenylhydrazines, ethyl acetoacetate, diethyl acetylenedicarboxylates and malononitrile (Scheme 2). It was evident that in absence of any catalyst the reaction was unable to proceed to give the expected product even after heating the reaction mixture for about 24 h (Table 1, entry 1) in aqueous medium at 60 °C. It is also noteworthy to mention that no product was detected when ZnO, nano Al_2O_3 and $InCl_3$ were applied for the four component coupling reaction (Table 1, entries 2, 3, 4). As shown in Table 1, the influence of Brønsted and Lewis acid catalysts ($H_6P_2W_{18}O_{62}$, $18H_2O$, *p*-toluenesulphonic acid, CF_3CO_2H and SiO_2) in the above reaction was marginal (entries 5, 6, 7, 8). Entries 9 and 10 in Table 1 clearly showed that Fe_2O_3 and CuO were superior to other conventional Brønsted and Lewis acid catalysts applied for the desired synthesis of dihydropyrano[2,3-*c*]pyrazole derivative (**5a**). From Scheme 1 it was evident that the reaction passes through two component (hydrazine and ethyl acetoacetate) condensation and Michael reaction (diethyl acetylenedicarboxylates and malononitrile) steps and probably Cu^{2+} catalyzes these two steps and Lewis acidic Fe^{3+} catalyzes the final intramolecular cyclization step. The above observations (Table 1, entries 9, 10) encouraged us to think about a catalyst having both metal ions, Fe^{3+} and Cu^{2+} to catalyze two component condensation, Michael reaction and intramolecular cyclization step concurrently. For this we advocated $CuFe_2O_4$ magnetic



Scheme 1 Retrosynthesis of dihydropyrano[2,3-*c*]pyrazole derivatives.

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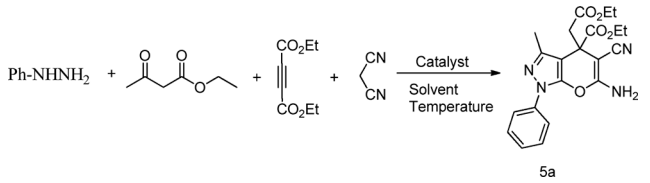

Scheme 2 Synthesis of dihydropyrano[2,3-*c*]pyrazole derivative.

nanoparticles for the MCR and to our delight $CuFe_2O_4$ spinel provided a satisfactory result (Table 1, entry 11). There is a maiden report[14c] for the L-proline catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives. One apparent advantage of the $CuFe_2O_4$ magnetic nanoparticles was that the catalyst catalyzed specific steps of the four component coupling reaction by using its explicit metal ions. Hence only the desired product was obtained with almost quantitative yield in a shorter reaction time. The non-recoverable organo catalysts generated larger amounts of bi-products by the polymerization of the catalyst and starting materials which in turn decreased the yield of the desired product and made the product purification complicated. The problems were resolved by using the magnetically retrievable nano-$CuFe_2O_4$.

In an effort to enhance the capacity of the chosen catalyst candidate we next sought to find the effect of different solvents (H_2O, MeOH, EtOH, CH_3CN and DMF) for the four component coupling protocol (Table 1, entries 11–15). The reaction using EtOH (81%) or H_2O (95%) as the solvents gave the corresponding product **5a** in high yields (Table 1, entries 11, 13). From the economical and environmental point of view, H_2O was chosen as the reaction medium for all further reactions.

Table 1 Optimization of reaction conditions for the synthesis[a] of dihydropyrano[2,3-*c*]pyrazole derivative **5a**

Entry	Catalyst	Catalyst load (mol%)	Solvent	Time (h)	Yield[b] %
1	—	10	H_2O	24	—
2	ZnO	10	H_2O	10	—
3	Nano Al_2O_3	10	H_2O	10	—
4	$InCl_3$	10	H_2O	10	—
5	$H_6P_2W_{18}O_{62}$, $18H_2O$	10	H_2O	6	18
6	*p*-Toluenesulphonic acid	10	H_2O	6	24
7	CF_3CO_2H	10	H_2O	6	14
8	SiO_2	10	H_2O	6	10
9	Fe_2O_3	10	H_2O	5	42
10	CuO	10	H_2O	5	30
11	Nano $CuFe_2O_4$	10	H_2O	2	95
12	Nano $CuFe_2O_4$	10	MeOH	3	61
13	Nano $CuFe_2O_4$	10	EtOH	2.5	81
14	Nano $CuFe_2O_4$	10	CH_3CN	3	49
15	Nano $CuFe_2O_4$	10	DMF	3	53
16	Nano $CuFe_2O_4$	3	H_2O	2	69
17	Nano $CuFe_2O_4$	5	H_2O	2	77
18	Nano $CuFe_2O_4$	8	H_2O	2	95

[a] All reactions were carried out with phenylhydrazines (1 mmol), ethyl acetoacetate (1 mmol), diethyl acetylenedicarboxylates (1 mmol), malononitrile (1 mmol) and specified catalyst in 5 ml solvent at 60 °C. [b] The yield of isolated products.

To find the optimized amount of magnetic nanoparticles for the four component coupling reaction, the reaction was carried out by varying the amount of the catalyst on the model reaction (Scheme 2). The conversion of dihydropyrano[2,3-*c*]pyrazole derivative **5a** increased linearly with the catalyst weight up to 8 mol% and became almost steady when the amount of catalyst was further increased beyond this. Therefore 8 mol% catalyst was sufficient to catalyze the reaction leading to expected heterocyclic molecules in excellent yield.

Nano $CuFe_2O_4$ was characterized by X-ray diffraction study, TEM, FT-IR spectra and EDX. The XRD patterns of $CuFe_2O_4$ calcined at 500 °C temperature is shown in Fig. 2. The crystalline nature of the spinel $CuFe_2O_4$ appears in the XRD pattern of the sample calcined at 500 °C. Six peaks at 18.3, 30.3, 35.6, 42.8, 57.1, and 62.98 can be assigned to the (101), (200), (211), (221), (303), and (224) diffraction peaks of $CuFe_2O_4$ spinel, respectively.[24] The morphology and microstructure of $CuFe_2O_4$ was investigated by HR-TEM (Fig. 3). The HR-TEM image reveals that the nanoparticle catalyst has a spherical shape and the nanoparticles are almost uniform in size with a narrow distribution. The size of the $CuFe_2O_4$ particles is approximately 15–18 nm. As shown in Fig. 4, the FT-IR spectra of $CuFe_2O_4$ calcined at 500 °C temperature clearly indicates the presence of the peaks (559 cm^{-1}) for the Fe–O stretching vibration.

Elemental analyses of the as-synthesized $CuFe_2O_4$ NPs were performed at EDX equipped onto TEM. Quantitative EDX

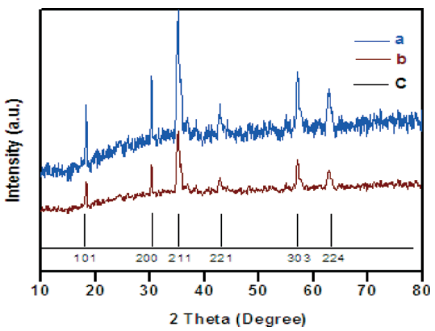

Fig. 2 XRD patterns of $CuFe_2O_4$ (a) before reaction and (b) after six run (c) crystal planes.

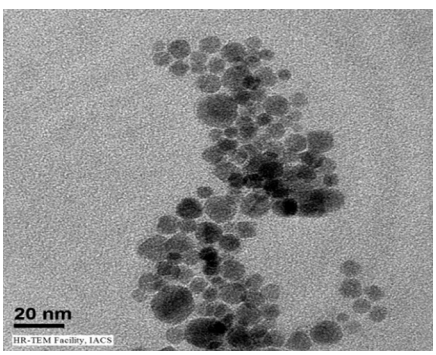

Fig. 3 HR-TEM image of $CuFe_2O_4$.

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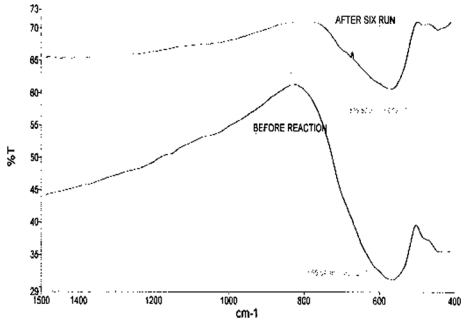

Fig. 4 FT-IR spectra of $CuFe_2O_4$ before reaction and after six run.

analysis showed Fe, Cu and O were the main elemental components (Fig. 5). The Cu–ferrite NPs analyzed as Fe = 29.28%, Cu = 13.99%, O = 56.69%. The analysis indicates that NPs in the array are of initial formula $CuFe_2O_4$.

The series of experiments revealed that the optimal results were obtained when phenylhydrazines (1 mmol), ethyl acetoacetate (1 mmol), diethyl acetylenedicarboxylates (1 mmol), malononitrile (1 mmol) and 8 mol% $CuFe_2O_4$ in 5 ml water was stirred at 60 °C for 2 h and the corresponding dihydropyrano[2,3-*c*]pyrazole derivative was obtained in 95% yield.

Under the established reaction conditions, the scope of the $CuFe_2O_4$-mediated synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives was investigated (Table 2). To delineate this approach, particularly in regard to library construction, this methodology was evaluated by using a variety of hydrazine derivatives, equipped with aryl-halo, aryl-nitro and aryl-cyano groups, ethyl acetoacetate, dialkyl acetylenedicarboxylates and alkyl nitriles. Five hydrazine derivatives, two dialkyl acetylenedicarboxylates and two alkyl nitrile derivatives (malononitrile and ethyl cyanoacetate) were chosen for the library construction. As revealed in Table 2, the reaction resulted in corresponding desired dihydropyrano[2,3-*c*]pyrazole derivatives by the tandem four-component condensation reaction in good to excellent yields in presence of nano-crystalline $CuFe_2O_4$.

Since pyran and coumarin framework show important bioactivities, we turned our attention to the synthesis of series of polyfunctionalized pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives. For this, dimedone, cyclohexane-1,3-dione and 4-hydroxycoumarin were examined to replace the active methylene intermediate I (Scheme 1) which was generated from substituted hydrazine and ethyl acetoacetate during the four component condensation reaction (Scheme 2). As revealed in Table 3, the reaction of dimedone or cyclohexane-1,3-dione or 4-hydroxycoumarin, (**6**) dialkyl acetylenedicarboxylates (**3**) and malononitrile or ethyl cyanoacetate (**4**) resulted in corresponding desired pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives in excellent yields.

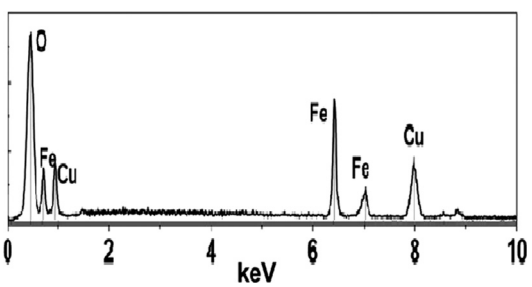

Fig. 5 EDX spectra of $CuFe_2O_4$ NPs.

After this successful endeavor with the synthesis of dihydropyrano[2,3-*c*]pyrazole, pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives, we changed the 1,3-diketo component from ethyl acetoacetate (**2**) to another equivalent of dialkyl acetylenedicarboxylate (Table 4). Interestingly, the one-pot reaction of substituted hydrazines, two equivalent dialkyl acetylenedicarboxylates and malononitrile produced new dihydropyrano[2,3-*c*]pyrazoles in the presence of nano $CuFe_2O_4$ (Table 4). The four component reaction passed through another intermediate (II or III, Scheme 3) which was more reactive than intermediate I (Scheme 1) due to the presence of electron withdrawing $-CO_2R$ group. Hence we were able to perform the reactions at room temperature. When R_2 and R_3 were different, four different sets of products (**9a–9d**, **9e–9h**, **9i–9l**, **9m–9p**) were isolated by using four hydrazine derivatives. During our studies on the scope of the reaction, it was found that the isolated yields of all the four products were almost the same in aqueous media. However different results were obtained when the reactions were performed in ethanol media. In ethanol media **9a**, **9e**, **9i** were the major products and **9c**, **9d**, **9g**, **9h**, **9k**, **9l** were the minor products. This observation led us to conclude that in ethanol media, intermediate II (releasing MeOH) was formed in greater extent than III (releasing EtOH), leaving a greater amount of unreacted diethyl acetylenedicarboxylate which in turn reacted with intermediate II to produce the major products (**9a**, **9e**, **9i**). Hence by introducing different solvents the yield of the products of this four component reaction could be changed. Unsubstituted hydrazine was very much reactive compared to substituted hydrazines and formed both the intermediates (II and III) in almost equal amount in ethanol and water. Hence in both the solvents, the yields of dihydropyrano[2,3-*c*]pyrazoles (**9m**, **9n**, **9o**, **9p**) were almost the same. This result is significant since there is no literature precedent for the synthesis of such highly functionalized dihydropyrano[2,3-*c*]pyrazoles.

According to our previous studies and the experimental results mentioned above, we proposed a possible mechanism (Scheme 3) for the 4CRs and 3CRs. The first step of the current 4CRs was the formation of pyrazolone intermediate (I, II, III ≡ **Y**) through Cu^{2+} (active species of nano-$CuFe_2O_4$)-promoted condensation of phenylhydrazine and ethyl acetoacetate or dialkyl acetylenedicarboxylate. Cu^{2+} of the magnetic nanoparticle ($CuFe_2O_4$) has shown excellent catalytic activity in promoting the condensation reaction for the formation of the intermediate **Y** by enhancing the electrophilicity of carbonyl groups of ethyl acetoacetate and polarizing the π-electron cloud of dialkyl acetylenedicarboxylate. Cu^{2+}

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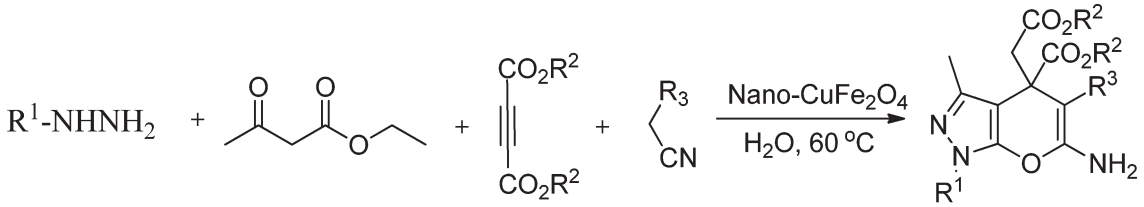
Table 2 Four component synthesis of 3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole derivatives



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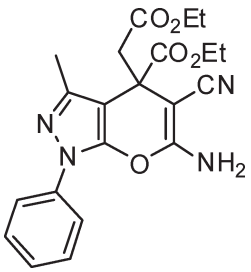
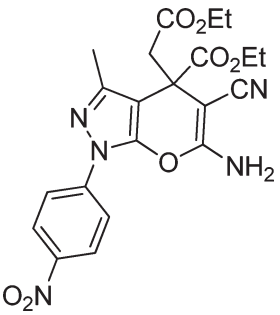
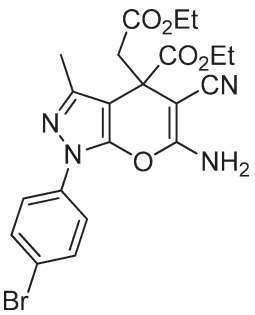


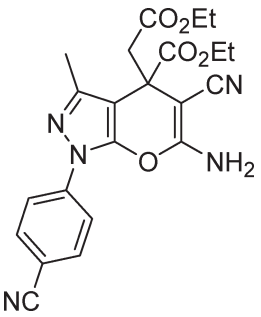
5a, 95%, 2.0 h



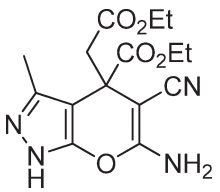
5b, 90%, 3.0 h



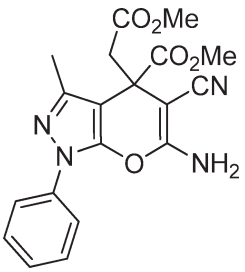
5c, 94%, 2.5 h



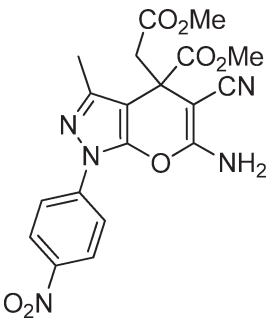
5d, 94%, 2.5 h



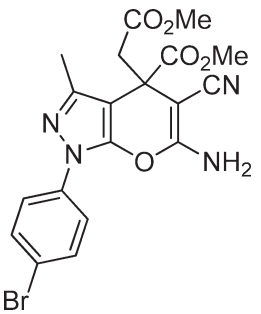
5e, 97%, 2.0 h



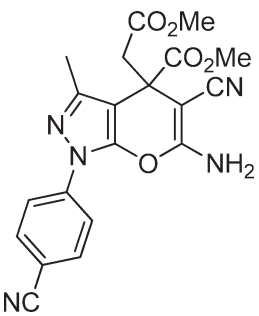
5f, 93%, 2.5 h



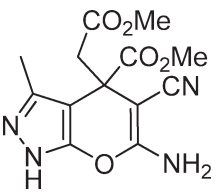
5g, 88%, 3.0 h



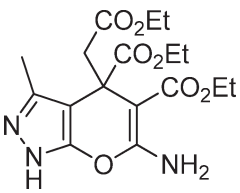
5h, 92%, 2.5 h



5i, 92%, 2.5 h



5j, 96%, 2.0 h



5k, 85%, 2.5 h

of $CuFe_2O_4$ also catalyzed the Michael addition reaction of dialkyl acetylenedicarboxylate with alkyl nitrile derivatives (malononitrile and ethyl cyanoacetate) during the formation of the intermediate **X**. The nucleophilic attack by the intermediate **Y** at the β position (with respect to nitrile group) of the intermediate **X** was enhanced by Cu^{2+} may be due to the polarization of the π-electron cloud. Finally, the Lewis acidic Fe^{3+} interacted with enolate intermediate **Z** which in turn facilitates intramolecular electrophilic cyclization with the formation of the six member ring (**P**). The nano-$CuFe_2O_4$ catalyzed activation of condensation, Michael reaction and subsequent ring annulations leading to the pyran derivatives were confirmed by the isolation of the intermediate **Y**.

The various products **5**, **7**, **9** thus obtained, were characterized by IR, ^1H and ^{13}C NMR spectroscopic analyses. Finally, the structures of three different type of synthesized heterocyclic core (3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole, pyrano[3,2-*c*]coumarin and alkyl-1,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylate derivatives) were confirmed by single-crystal X-ray diffraction of three representative compounds **5j**, **7i**, **9a** (Fig. 6–8).[25]

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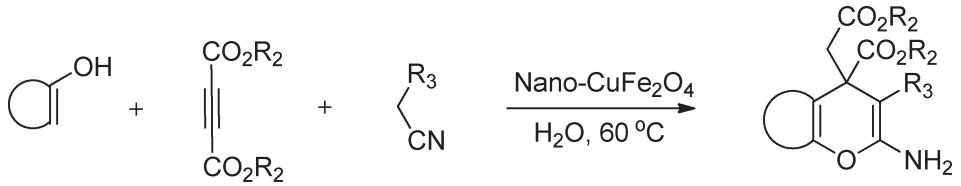
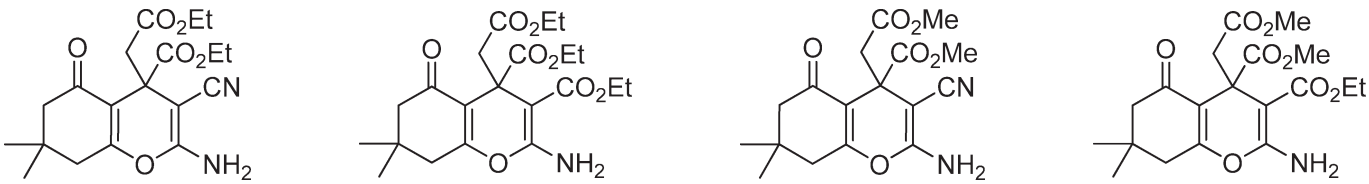
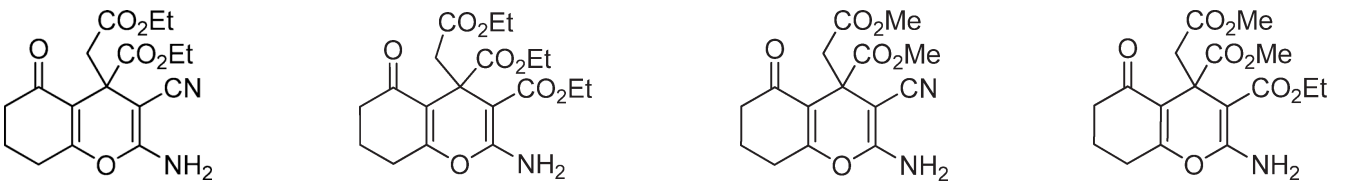
Table 3 Synthesis of pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives



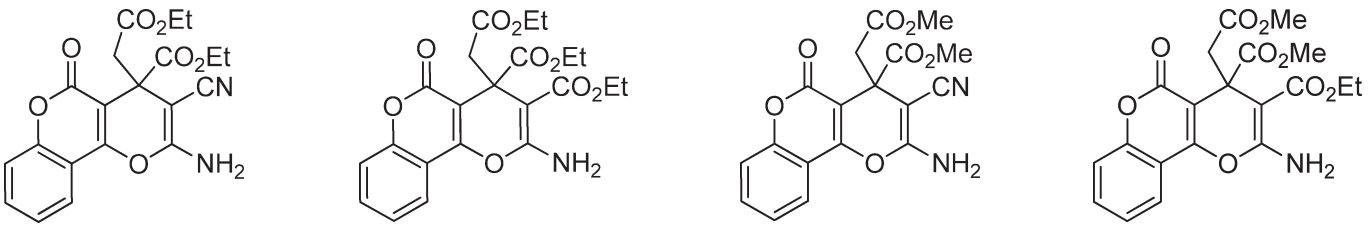
6 3 4 7



7a, 92%, 2.0 h **7b**, 88%, 2.5 h **7c**, 91%, 2.0 h **7d**, 86%, 2.5 h



7e, 94%, 2.0 h **7f**, 89%, 2.5 h **7g**, 92%, 2.0 h **7h**, 86%, 2.5 h



7i, 90%, 2.5 h **7j**, 87%, 3.0 h **7k**, 88%, 2.5 h **7l**, 84%, 3.0 h

A heterogeneous catalyst is more interesting when it can be easily recovered and re-used. Separation of the catalyst and isolation of the desired product from the reaction mixture is one of the most crucial aspects of organic synthesis. Catalyst recovery, which is generally performed by filtration, is relatively inefficient. Another technique, extractive isolation of products, also requires excessive amounts of organic solvents. However, in the aforementioned protocol, after completion of the reaction, water was removed under reduced pressure from the reaction mixture and was stirred with 5 mL ethanol and within a few seconds after stirring was stopped, the catalyst was deposited on the magnetic bar and then easily removed using an external magnet, leaving a clear reaction mixture. The recovered catalyst was then washed with ethanol and distilled water and dried under vacuum. The catalyst was recovered in excellent yield (92–97%) after each of the new set of reaction. This recycled catalyst was used for the synthesis of dihydropyrano[2,3-*c*]pyrazole applying the developed protocol. For this purpose, the reusability of the catalyst was tested for the reaction of phenylhydrazines, ethyl acetoacetate, diethyl acetylenedicarboxylates and malononitrile (Scheme 2). The catalyst was found to be reusable for at least six cycles without any considerable loss of activity. We also investigated the structural stability of $CuFe_2O_4$ catalyst by comparing its XRD and FT-IR spectra before and after six run in the one-pot synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives (**5a**). The results obtained are illustrated in Fig. 2 and 4 respectively. It can be seen that the XRD and FT-IR spectra of the catalyst obtained before and after six run was almost same indicating that the MSNPs was structurally stable under the applied reaction conditions.

Conclusions

Overall, we have succeeded in developing a novel, convenient and efficient protocol for the preparation of dihydropyrano[2,3-*c*]pyrazole, pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives using readily available starting materials by tandem one-pot four- and three-component reaction. Again this protocol, combining construction and modification of the dihydropyrano[2,3-*c*]pyrazole skeleton, increases the structural diversity of the final products by forming a new library of dihydropyrano[2,3-*c*]pyrazole derivatives. The nano-catalyst system encompassing a paramagnetic core allows rapid and selective chemical transformations

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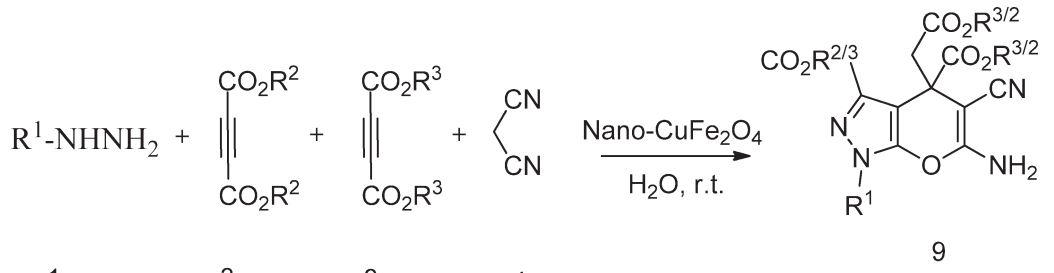
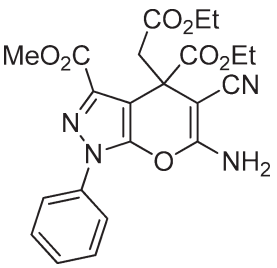
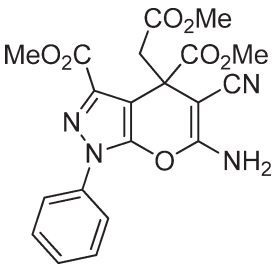
Table 4 Four component synthesis of alkyl-1,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylate derivatives



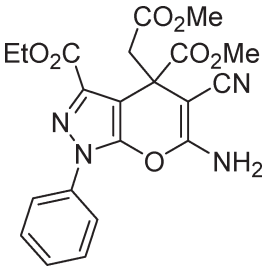
1 3 3 4



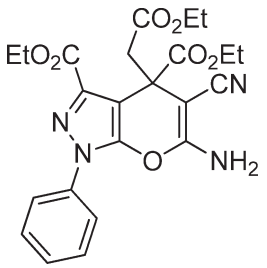
9a, 23%,[a] 42%,[b] 4.0 h



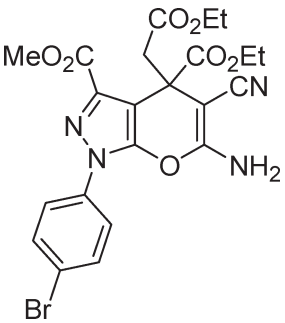
9b, 26%,[a] 34%,[b] 4.0 h



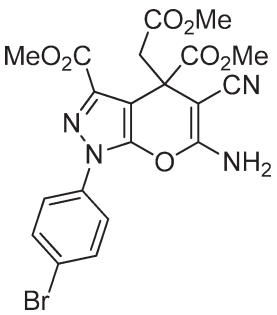
9c, 25%,[a] 11%,[b] 4.0 h



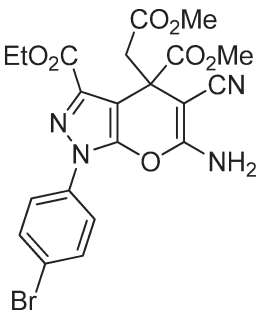
9d, 26%,[a] 13%,[b] 4.0 h



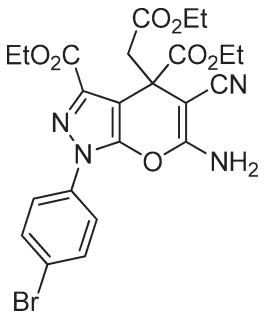
9e, 26%,[a] 43%,[b] 4.0 h



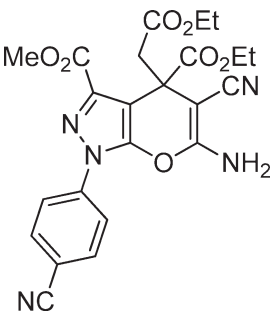
9f, 27%,[a] 31%,[b] 4.0 h



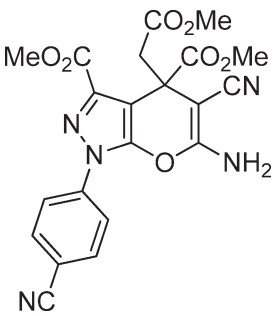
9g, 25%,[a] 13%,[b] 4.0 h



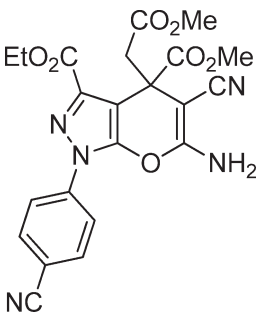
9h, 22%,[a] 13%,[b] 4.0 h



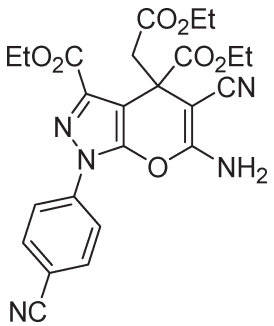
9i, 25%,[a] 42%,[b] 4.0 h



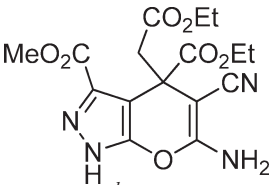
9j, 24%,[a] 33%,[b] 4.0 h



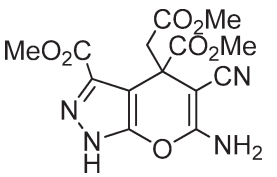
9k, 25%,[a] 13%,[b] 4.0 h



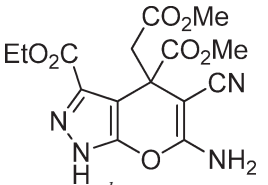
9l, 26%,[a] 12%,[b] 4.0 h



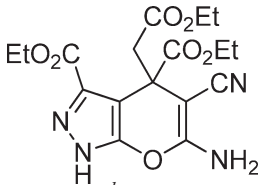
9m, 24%,[a,b] 2.0 h



9n, 26%,[a,b] 2.0 h



9o, 23%,[a,b] 2.0 h



9p, 27%,[a,b] 2.0 h

[a] Isolated yield of the when the reaction was performed in water. [b] Isolated yield of the when the reaction was performed in EtOH.

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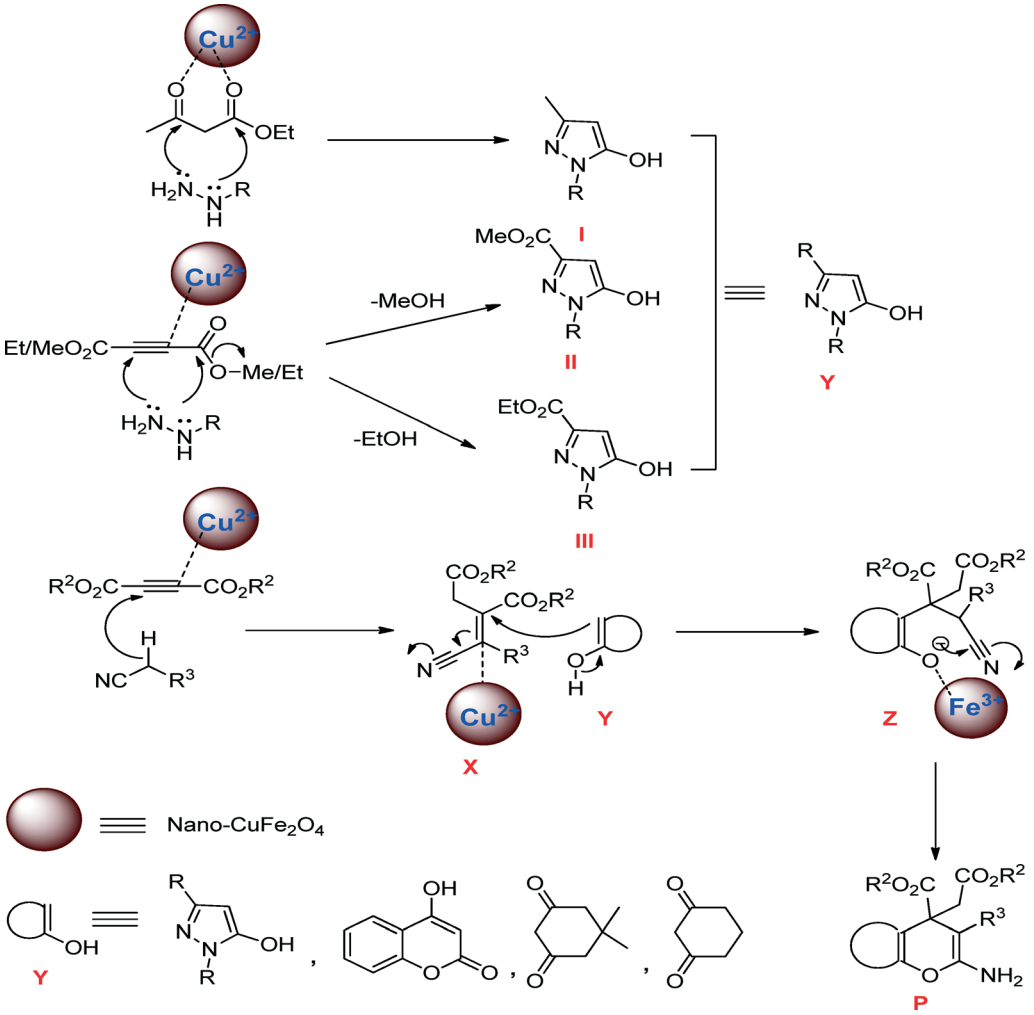

Scheme 3 The proposed mechanisms for the formation of the products (**5**, **7**, **9**).

with excellent product yield. The use of $CuFe_2O_4$ magnetic nanoparticles as catalyst solves the basic problems of catalyst separation. This is a promising approach from sustainable and practical chemistry viewpoints. We believe that the convenient and efficient $CuFe_2O_4$ catalyzed 4CRs and 3CRs, the mechanism and the interesting activities of the catalyst described here will be helpful for practical application and a new protocol design.

Experimental

Preparation of catalyst

$CuFe_2O_4$ was prepared by using a simple modified literature method.[26] $Fe(NO_3)_3{\cdot}9H_2O$ (4 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (2 mmol) and citric acid (9 mmol) were dissolved completely in distilled water (50 mL). The solution was heated up to 90 °C to

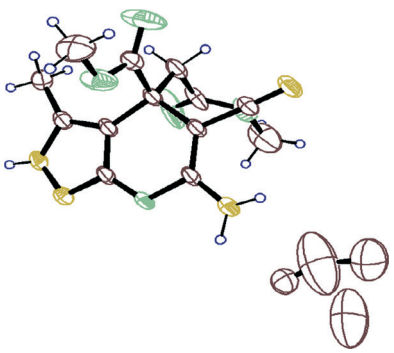

Fig. 6 ORTEP diagram of compound **5j** (CCDC no. 959948).

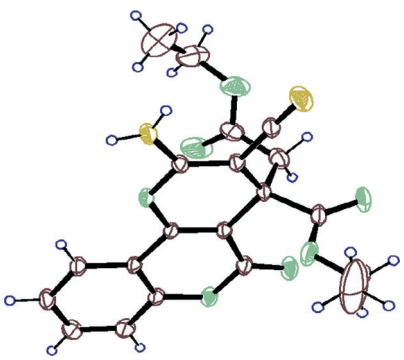

Fig. 7 ORTEP diagram of compound **7i** (CCDC no. 959885).

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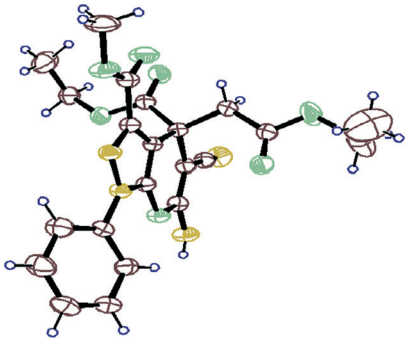

Fig. 8 ORTEP diagram of compound **9a** (CCDC no. 968630).

evaporate the water in an oil bath under continuous stirring and the citric acid was then decomposed at 300 °C. After the reaction, the resultant powder was calcined at 500 °C for 2 h to give the $CuFe_2O_4$ samples.

General procedure for the synthesis of 3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole derivatives

A mixture of substituted hydrazines (1 mmol), ethyl acetoacetate (1 mmol), dialkyl acetylenedicarboxylates (1 mmol), malononitrile or ethyl cyanoacetate (1 mmol) and $CuFe_2O_4$ (8 mol%) was stirred at 60 °C for a required period of time (TLC). After completion of the reaction, water was removed under reduced pressure from the reaction mixture and was stirred with 5 mL ethanol and within a few seconds after stirring was stopped, the catalyst was deposited on the magnetic bar and removed using an external magnet, leaving a clear reaction mixture. After removing the catalyst the solvent was evaporated under vacuum to give the crude product, which was purified by column chromatography.

General procedure for the synthesis of pyrano[3,2-*c*]coumarin and 4*H*-chromene derivatives

A mixture of dimedone or cyclohexane-1,3-dione or 4-hydroxycoumarin (1 mmol), dialkyl acetylenedicarboxylates (1 mmol) and malononitrile or ethyl cyanoacetate (1 mmol) and $CuFe_2O_4$ (8 mol%) was stirred at 60 °C for a required period of time (TLC). After completion of the reaction, water was removed under reduced pressure from the reaction mixture and was stirred with 5 mL ethanol and within a few seconds after stirring was stopped, the catalyst was deposited on the magnetic bar and removed using an external magnet, leaving a clear reaction mixture. After removing the catalyst the solvent was evaporated under vacuum to give the crude product, which was purified by column chromatography.

General procedure for the synthesis of alkyl-1,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylate derivatives

A mixture of substituted hydrazines (1 mmol), dialkyl acetylenedicarboxylates (1 mmol + 1 mmol), malononitrile (1 mmol) and $CuFe_2O_4$ (8 mol%) was stirred at room temperature for a required period of time (TLC). After completion of the reaction, water was removed under reduced pressure from the reaction mixture and was stirred with 5 mL ethanol and within a few seconds after stirring was stopped, the catalyst was deposited on the magnetic bar and removed using an external magnet, leaving a clear reaction mixture. After removing the catalyst the solvent was evaporated under vacuum to give the crude product, which was purified by column chromatography.

Acknowledgements

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