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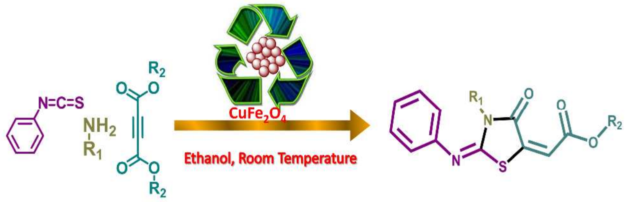

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ARTICLE

A facile and efficient synthesis of functionalized 4-oxo-2-(phenylimino)thiazolidin-5-ylideneacetate derivatives via $CuFe_2O_4$ magnetic nanoparticles catalyzed regioselective pathway

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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Nano-$CuFe_2O_4$ spinel has been found to enforce strong catalytic activity in facilitating the cascade reaction involving 1,4-addition and intramolecular electrophilic cyclization in a perfectly regiocontrolled manner and a series of functionalized 4-oxo-2-(phenylimino)thiazolidin-5-ylideneacetate derivatives were generated successfully. The reaction is mild and selective with good to high yields and displays significant functional group tolerance. The dual role of thiocarbonyl moiety as an electrophile and as nucleophile has been observed in this three component coupling reaction. $CuFe_2O_4$ magnetic nanoparticles were prepared by a simple and effective citric acid complex method and characterized by using XRD, FT-IR, and TEM image. The catalyst was recycled for six cycles without any loss of 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, tedious workup and purification hazards.

Introduction

In recent years, much attention has been directed toward the synthesis of thiazolidinone compounds owing to their tremendous application in various research fields including biological science and medicinal chemistry. Thiazolidinone core containing compounds are acknowledged as antidiabetic[1], anticancer[2], calcium-channel blocker[3,4], platelet activating factor (PAF) antagonist[5] and anti-HIV[6] activity. Also, 2-iminothiazolidin-4-ones exhibit outstanding hypnotic[7,8], antitubercular[9], cardiovascular[10] and cyclooxygenase (COX) inhibitory[11] activities (Figure 1).

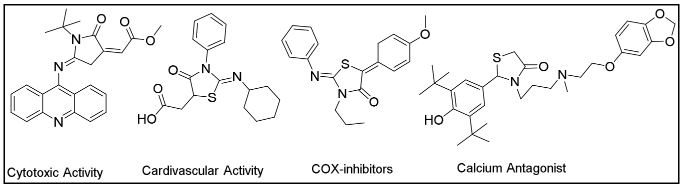


Figure 1: Structures of some biologically relevant thiazolidinone scaffolds

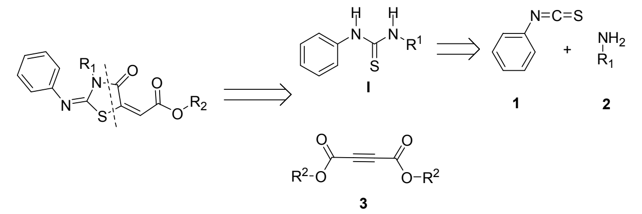
The relevance of these structural motifs has constituted the focus of many investigations regarding improved strategies for their synthesis. In the literature, several strategies for the synthesis of thiazolidines and thiazolidinone are known. A general approach toward 2-iminothiazolidin-4-ones12-14 involves cyclization of thioureas with α-halocarboxylic acids,15 acyl halides,[16,17] carboxylic esters[18] or the condensation reaction of the appropriate amine, aldehyde and mercapto acids[6]. The vast biological importance of thiazolidinone derivatives inspired us to develop a novel protocol for the efficient synthesis of 4-oxo-2-(phenylimino)thiazolidin-5-ylideneacetates.

It is widely accepted that a smaller catalyst particle means a higher activity.[19] As a result, both the activity and the stability of a solid catalyst suspended in a liquid media can benefit greatly from the use of small catalyst 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. The efficient separation and subsequent recycling of homogeneous transition metal catalysts remain scientific challenges of economical and ecological relevance. 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 with an external magnet. Other exciting properties of these magnetic materials include their highly active and specific centers of ultrasmall size coupled with their high specificities; 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.[20-22] There has been an increasing trend toward the use of MSNPs in increasingly efficient green chemical synthesis.

It can be anticipated that the advantages of MSNPs can be further utilized in organic transformations. As part of a program aimed at developing novel heterocyclic systems applying magnetic nanoparticles,[20c,d, 23] herein we would like to demonstrate an efficient $CuFe_2O_4$ catalyzed regioselective cascade reaction for the preparation of functionalized 4-oxo-2-(phenylimino)thiazolidin-5-ylideneacetate derivatives. In our previous works[20c,d] we synthesized $CuFe_2O_4$ nano catalyst by hydrothermal technique and was characterized by XRD, TEM and FT-IR spectra. The synthesized catalyst was applied in knoevenagel condensation, Michael addition and intramolecular cyclization reaction for the synthesis of pyrrole core containing heterocyclic scaffolds, dihydropyrano[2,3-c]pyrazol, pyrano[3,2-c]coumarin and 4H-chromene derivatives. In this paper we have shown a new application of the nano- CuFe2O4.

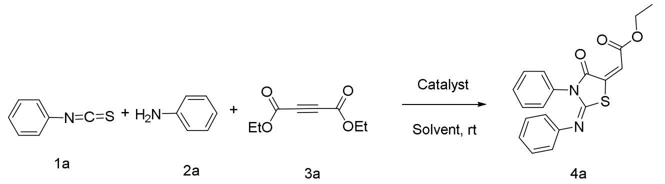
Results and discussion

Due to very high biological potential, our efforts were directed in exploring simple and efficient method for the synthesis of substituted 2-iminothiazolidin-4-one derivatives core. We tried to synthesize 2-iminothiazolidin-4-one derivatives by advocating a three component coupling reaction of phenyl isothiocyanate (1) and amine (2) and dialkyl acetylenedicarboxylates (3, Scheme 1).



Scheme 1. Retrosynthesis of 2-iminothiazolidin-4-one derivatives

At the onset of our investigation, the reaction of phenyl isothiocyanate (1a), aniline (2a) and diethyl acetylenedicarboxylate (3a) was selected as the prototypical precursors to screen the experimental conditions in the presence of a variety of catalysts. The effects of various reaction conditions on the cascade cyclization are summarized in Table 1.



Scheme 2. Synthesis of 2-iminothiazolidin-4-one derivative

In order to find the best reaction conditions for the synthesis of 2-iminothiazolidin-4-one derivatives, our preliminary investigations focused on the search for a suitable catalyst. At the onset of our studies, we tested different Brønsted and Lewis acid catalysts like nano Al_2O_3, nano ZnO, acetic acid, L-proline, PTSA, $BF_3{\cdot}Et_2O$, $InCl_3$ and AgOTf (Table 1, entry 2-9) for the three-component reaction of phenyl isothiocyanate (1a) and aniline (2a) with diethyl acetylenedicarboxylate (3a) (Scheme 2). It was noteworthy to mention that the influence of the Brønsted and Lewis acid catalysts in the above reaction was not very much pronounced and very poor yield of the desired product was obtained. It was also evident that in absence of any catalyst the reaction was unable to proceed to give the expected product even after stirring the reaction mixture for about 8 h (Table 1, entry 1) in ethanol medium at room temperature. Entries 10 and 11 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 2-iminothiazolidin-4-one derivatives (4a). Retrosynthetic analysis of 2-iminothiazolidin-4-one derivatives (scheme 1) clearly indicated that the synthesis involved uncatalyzed two component condensation of phenyl isothiocyanate and aniline to produce intermediate (I) and Michael reaction of diethyl acetylenedicarboxylate and intermediate (I). Probably Cu^{2+} catalyzes the Michael reaction step and Lewis acidic Fe^{3+} catalyzes the final intramolecular cyclization step. The above observations (Table 1, entries 10, 11) encouraged us to think about a catalyst having both metal ions, Fe^{3+} and Cu^{2+} to catalyze the Michael reaction and intramolecular cyclization step concurrently. For this we advocated $CuFe_2O_4$ magnetic nanoparticles for the MCR which provided satisfactory result

(Table 1, entry 12). One apparent advantage of the $CuFe_2O_4$ magnetic nanoparticle was that the catalyst catalyzed specific steps of the three component coupling reaction by using its explicit metal ions. Hence only the desired product was obtained with almost quantitative yield in shorter reaction time.

Table 1: Optimization of reaction conditions[a]

Entry	Catalyst	Catalyst load (mol%)	Solvent	Time	Yield (%)[b]
1	_	_	EtOH	8h	trace
2	Nano Al_2O_3	10	EtOH	12h	3
3	Nano ZnO	10	EtOH	12h	5
4	Acetic acid	10	EtOH	12h	15
5	L-proline	10	EtOH	12h	trace
6	PTSA	10	EtOH	12h	10
7	$BF_3·Et_2O$	10	EtOH	10h	8
8	$InCl_3$	10	EtOH	10h	12
9	AgOTf	10	EtOH	10h	trace
10	Fe_2O_3	10	EtOH	45min	45
11	CuO	10	EtOH	45min	39
12	**Nano $CuFe_2O_4$**	**10**	**EtOH**	**30min**	**94**
13	Nano $CuFe_2O_4$	10	DCM	45min	73
14	Nano $CuFe_2O_4$	10	DMF	45min	61
15	Nano $CuFe_2O_4$	10	CH_3CN	45min	70
16	Nano $CuFe_2O_4$	10	H_2O	45min	78
17	Nano $CuFe_2O_4$	5	EtOH	30min	75
18	Nano $CuFe_2O_4$	8	EtOH	30min	83
19	Nano $CuFe_2O_4$	15	EtOH	30min	94

[a]Reaction conditions:1a (1 mmol), 2a (1 mmol), 3a (1 mmol)and specified catalyst were stirred in 5ml solvent at room temperature

[b] Yield of isolated products

In an effort to enhance the capacity of the chosen catalyst candidate we next sought to find the effect of different solvents (EtOH, DCM, DMF, CH_3CN & H_2O) for the four component coupling protocol (Table 1, entries 12-16). The reaction using EtOH as the solvent gave the corresponding product 4a in high yield (Table 1, entries 12). Hence, EtOH was chosen as the reaction medium for all further reactions.

To find the optimized amount of magnetic nanoparticles for the three component coupling reaction, the reaction was carried out by varying the amount of the catalyst on the model reaction (Scheme 2). The conversion of 2-iminothiazolidin-4-one derivative (4a) increased linearly with the catalyst weight up to 10 mol% and became almost steady when the amount of catalyst was further increased beyond this. Therefore 10 mol% catalyst was sufficient to catalyze the reaction.

Nano $CuFe_2O_4$ was characterized[20c,d] by X-ray diffraction study, TEM and FT-IR spectra. The XRD patterns of nano $CuFe_2O_4$ spinel calcined at 500 °C temperature is shown in Figure 2. Crystalline nature of the $CuFe_2O_4$ spinel appears in the XRD pattern of the sample calcined at 500 °C. Five 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.

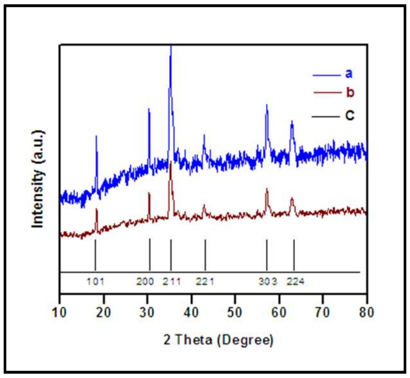


Figure 2. XRD patterns of $CuFe_2O_4$ (a) before reaction and (b) after six run

(c) Crystal planes according to standard JCPDS (No. 06–0545) data

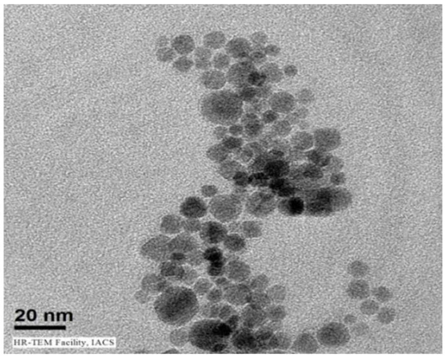


Figure 3. HR-TEM image of $CuFe_2O_4$

The morphology and microstructure of $CuFe_2O_4$ was investigated by HR-TEM (Figure 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 Figure 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.

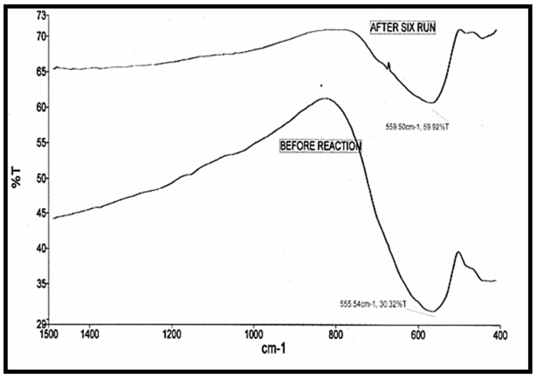


Figure 4: FT-IR spectra of $CuFe_2O_4$ before reaction and after six run

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

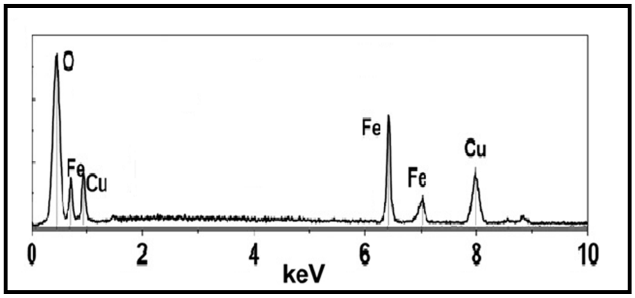
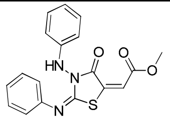


Figure 5: EDX spectra of $CuFe_2O_4$ NPs

Initializing the optimal conditions, the scope and limitations were further investigated to evaluate the efficiency of nano-$CuFe_2O_4$ catalyst. The results are summarized in Table 2. In general, the reactions proceeded smoothly in the presence of diethyl acetylenedicarboxylate or dimethyl acetylenedicarboxylate. To prove the ability of the method and to introduce further structural diversity, a large variety of electronically and structurally divergent aromatic amines were introduced. All these compounds responded very well and satisfactory yields of the desired product were achieved. The protocol also worked efficiently in case of acid and base sensitive heteroaromatic amines and aliphatic amines as well. Thus it is pertinent to mention that a library of 4-oxo-2-(phenylimino)thiazolidin-5-ylideneacetate derivatives were synthesized from good to excellent yields within a very short period of time. The structures of the desired products were characterized by IR, ^1H, ^{13}C NMR as well as HRMS spectral data and it was further established from single-crystal X-ray diffraction study (Figure 6a, 6b).

Table 2: Substrate Scope[a]

4a, 30min, 94%	4b, 25min, 93%	4c, 35min, 92%
4d, 20 min, 98%	4e, 30 min, 91%	4f, 25min, 95%
4g, 25min, 93%	4h, 20min, 97%	4i, 20min, 96%
 4j, 30min, 94%	4k, 25 min, 92%	4l, 30min, 95%

[a] Reaction conditions: 1 (1 mmol), 2 (1 mmol), 3 (1 mmol), nano-$CuFe_2O_4$ (10 mol%), 5 ml ethanol, room temperature

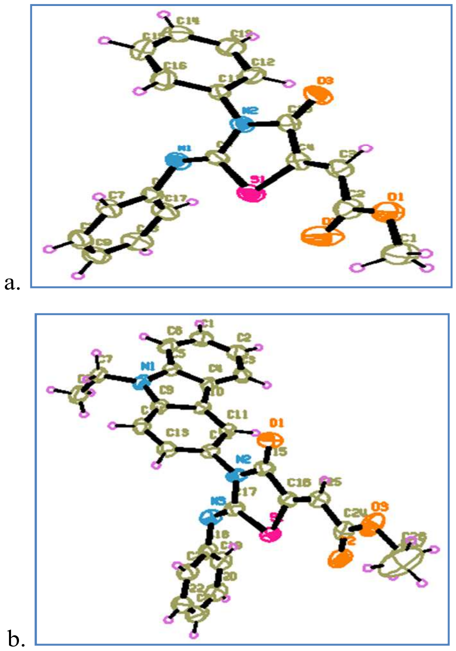
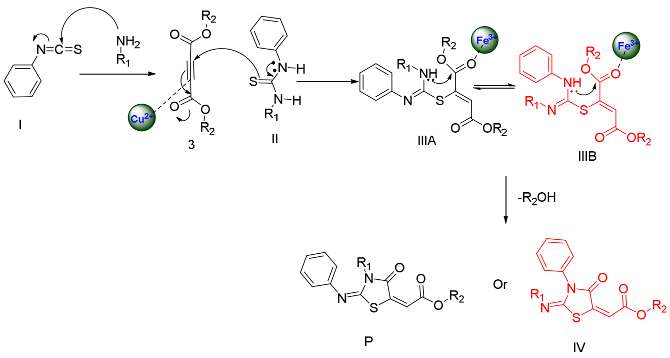


Figure 6: (a) ORTEP diagram of the single-crystal X-ray structure of the product 4f (CCDC 958279) (b) ORTEP diagram of the single-crystal X-ray structure of the product 4e (CCDC 977594)

On the basis of these results, a probable mechanism for this three component reaction is presented in Scheme 3. The reaction proceeds instantaneously between phenyl isothiocyanate and amine derivatives leading to the initial formation of the intermediate N, N′-diphenylthiourea (**II**). The attack of amine nucleophiles to the thiocarbonyl moiety occurs smoothly even without the presence of catalyst which proves the highly electrophilic nature of the thiocarbonyl moiety. In the next step, Cu^{2+} of $CuFe_2O_4$ catalyzes the Michael addition reaction of N, N′-diphenylthiourea (**II**) and acetylenic ester (3) during the formation of the intermediate **IIIA**. The nucleophilic attack by the N, N′-diphenylthiourea (**II**) to acetylenic ester is enhanced by Cu^{2+} may be due to the polarization of the π-electron cloud. In this particular step thiocarbonyl moiety operates as nucleophile and this dual character of the thiocarbonyl moiety directed the reaction towards the synthesis of thiazolidinone scaffolds. Intermediate **IIIA** can undergo tautomerization to form intermediate **IIIB**. Finally Fe^{3+} interacts with intermediate **IIIA** & **IIIB** to generate an electron-deficient complex, which undergoes intramolecular electrophilic cyclization with the formation of two regioisomers (**P** & **IV**). But in practice only the regioisomer **P** was isolated under the developed synthetic protocol which was unambiguously confirmed by single-crystal X-ray diffraction study (Fig. 6b). Probably intermediate **IIIA** was unable to undergo tautomerization to form intermediate **IIIB** under this very mild catalytic condition which in turn made the synthetic rout very immaculate, regiocontrolled and high yielding.



Scheme 3. Plausible mechanistic pathway

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, within a few seconds after stirring was stopped, catalyst was deposited on the magnetic bar and then easily removed using an external magnet, leaving the 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 (91-97%) after each of the new set of reaction. This recycled catalyst was used for the synthesis of 2-iminothiazolidin-4-one derivatives applying developed protocol. For this purpose, the reusability of catalyst was tested for the reaction of phenyl isothiocyanate (1a) and aniline (2a) with diethyl acetylenedicarboxylate (3a) (Scheme 2). The catalyst was found to be reusable for at least six cycles without 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 2-iminothiazolidin-4-one derivative (4a). The results obtained are illustrated in Fig. 2 and Fig. 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 2-iminothiazolidin-4-one derivatives using readily available starting materials by tandem one-pot three-component reaction. The nano-catalyst system encompassing a paramagnetic core allows rapid and selective chemical transformations in a regiocontrolled way resulting satisfactory product yield. This methodology might provide a new strategy for constructing new heterocycles and this simple, environmentally benign and convenient methodology extends the scope towards a wide spectrum of novel compounds possessing an important structural subunit of a variety of biologically active molecules.

Acknowledgement

We acknowledge the financial support from the University of Calcutta. G. P. thanks CSIR, New Delhi, India for her fellowship (Grant No. 09/028(0792)/2010 EMR-I), S. P. thanks UGC New Delhi, India for his fellowship. Crystallography was performed at the DST-FIST, India-funded Single Crystal Diffractometer Facility at the Department of Chemistry, University of Calcutta.

General Procedure for the synthesis of 4-oxo-2-(phenylimino)thiazolidin-5-ylideneacetate Derivatives:

A solution of phenyl isothiocyanate (1mmol), aniline (1mmol), acetylenic ester (1mmol) and nano $CuFe_2O_4$ (10 mol%) in ethanol (5ml) was stirred at room temperature. After completion of the reaction (analyzed by TLC), catalyst was deposited on the magnetic bar and then easily removed by using an external magnet, leaving the clear reaction mixture. Then the solvent was removed from the reaction mixture under reduced pressure to get the crude product which was purified by column chromatography (silica gel 100-200 mesh). All compounds were well characterized by ^1H, ^{13}C NMR, FT-IR and HRMS analysis.

Notes and references

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†Electronic Supplementary Information (ESI) available: [Experimental details and spectroscopic data for all compounds]. See DOI: 10.1039/b000000x/

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