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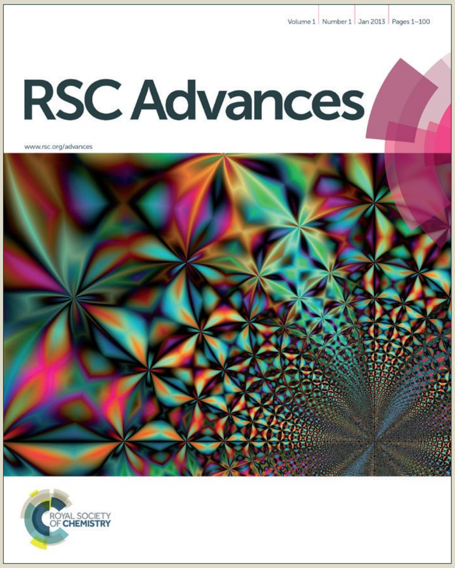

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ARTICLE TYPE

BF_3/nano-sawdust as a green, biodegradable and no expensive catalyst for synthesis of highly substituted dihydro-2-oxopyrroles

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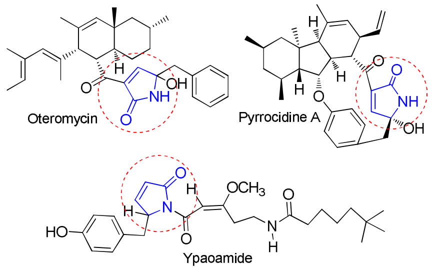
Received (in XXX, XXX) XthXXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

BF_3/nano-sawdust was used as a readily available, inexpensive, biodegradable and environmentally benign heterogeneous solid acid catalyst for the one pot cascade synthesis of highly functionalized dihydro-2-oxypyrroles. Four-component reactions (4CRs) of the dialkylacetylenedicarboxylates, primary amines and aldehydes were used for synthesis of these compounds under thermal conditions.

Introduction

Dihydro-oxopyrrole(DPO) derivatives are important structures exhibit biological activities such as herbicidal,[1] antitumor,[2] pesticidal,[3] anti-HIV,[4] antibiotics,[5] antimalarial[6]and its derivatives are crucial core structures used to create many natural products like bilirubins,[7] oteromycin,[8]ypaoamide[9]andpyrrocidine A[10](Scheme 1).



Scheme1. The structure of some natural compounds with dihydro-2-oxopyrrole motif.

Due to the wide range application of dihydro-oxopyrrole derivatives in pharmaceuticals, agrochemicals, and natural products, their synthesis remains an area of intense current interest to the chemical synthesis. A number of synthetic routes have been developed for the synthesis of dihydro-oxopyrrole, including ruthenium-catalyzed reaction of α,ß-unsaturated imines with carbon monoxide and ethylene,[11] reaction of isocyanides, dialkylacetylenedicarboxylates, and benzoyl chlorides,[12] carboamination/oxidative cyclization of C-acylimines with alkenes,[13] transannulation of 1-sulfonyl-1,2,3-triazole with ketene silylacetal,[14] reaction of acetylene with imines, and CO_2,[15] Pd-catalyzed cyclization of ethyl glyoxalate and amines[16] and reaction of α-cyanomethyl-ß-ketoesters and alcohols.[17] Among these versatile synthetic methods, multicomponent reactions (MCRs) have attracted particular attention;[18] A few methods have been reported for the synthesis of dihydro-2-oxopyrroles using MCRs such as four component reaction of dialkylacetylenedicarboxylate, aldehyde, and amines. Previously, this protocol has been catalyzed by TiO_2-nanopowder,[19] I_2,[20] *p*-toluenesulfonic acid,[21] $Cu(OAc)_2{\cdot}H_2O$/salicylic acid,[22] AcOH,[23] 1-methyl-2-oxopyrrolidinium hydrogen sulfate ([Hpyro][HSO_4]),[24] $InCl_3$[25] and [n-Bu_4N][HSO_4].[26]
Some of these catalysts have many limitations such as inefficient separation of the catalyst from homogeneous reaction mixtures,[20-23] unrecyclable and environmentally limitations.[20-25] Hence, development of new solid acids with numerous advantages such as cost-effectiveness, environmentally benign, easy workup and good stability for one-pot multicomponent synthesis of highly substituted dihydro-oxopyrrole scaffolds is still in demand. In this regard, our aim is developing cheap and biomaterials solid acid catalysts for this transformation.

Cellulose is one of the most abundant natural carbon based biopolymers containing free OH groups with nucleophilic character. It has been used for synthesis of some compounds which used in enantioselective chromatography,[27] protein immobilization,[28] antibodies[29] and retarded drug release.[30]

Sawdust is a biodegradable, natural, cheap, renewable and readily available source of cellulose.

In this work, we have investigated about synthesis of sawdust based catalyst by bonding Lewis acids to OH groups of D-glucose units. Since, sawdust is containing cellulose with other substances such as pectin, tannin, proteins, minerals and lignin that caused leaching in organic mediums. Therefore, pectin, lignin, proteins and minerals must be removed. For this purpose the pine sawdust was treated respectively with NaOH, NaClO, and H_2O_2. For preparation of nano-sawdust, the sawdust has been treated with concentrated H_2SO_4 for partial hydrolysis of its cellulose. Then, the nano-sawdust was used to synthesis of BF_3/nano-sawdust as a new, biodegradable and green catalyst.

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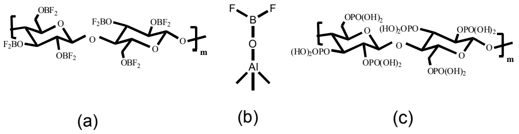
We wish to report herein its catalytic behavior for the cost-effective and facile one pot cascade synthesis of highly functionalized dihydro-2-oxopyrroles via 4CRs of the dialkylacetylenedicarboxylates, amines and aldehyde under thermal conditions.

Result and discussion

In order to investigate the structure of BF_3/nano-sawdust, we have studied the FT-IR (ATR) spectra of pine sawdust and BF_3/nano-sawdust (Figure 1). In sawdust FT-IR spectrum, two strong bands at 3331 and 1020 cm-1 were observed. In BF_3/nano-sawdust, in addition to the above mentioned bands, some bands also appeared at 820, 913, 1264, 1424 and 1633 cm-1. The band in 916 cm^{-1} verifies the C-O-B group on BF_3/nano-sawdust.

The proposed structure containing possible model for acid sites formed on the catalyst is similar to the reported structure for cellulose triphosphate gels that was prepared by phosphorylation of trihydroxy[31] groups of D-glucose units and BF_3/γ-Al_2O_3 (Scheme 2).[32]



(a) (b) (c)

Scheme 2. Proposed structure for (a) BF_3/nano-sawdust, (b)BF_3/γ-Al_2O_3 and (c) cellulose triphosphate

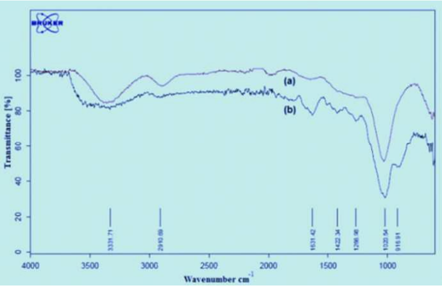


Fig 1: FT-IR (ATR) spectrum of (a) pine sawdust and (b) BF_3/nano-sawdust.

The FESEM image of nano-sawdust and BF_3/nano-sawdust is shown in figure 2. According to the FESEM date, the particles size of catalyst is below 50 nm. Quantitative elemental information (EDS) of BF_3/nano-sawdust was measured by SEM/EDS instrument, Phenom pro X, (Figure 3). According to this data, the weight percentage of F, O and C are 46.4, 39.3 and 7.9, respectively.

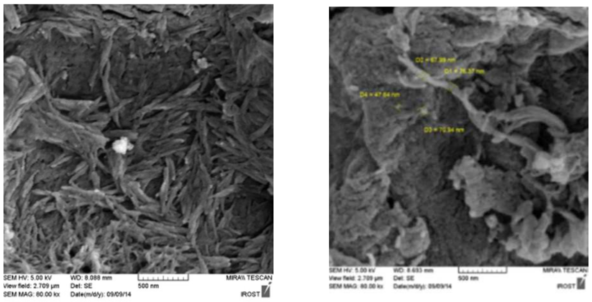


Fig 2. The FESEM image of (a) nano-sawdust and (b) BF_3/nano-sawdust

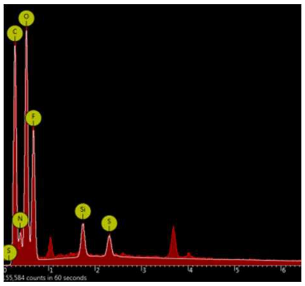
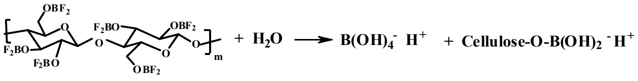


Fig. 3: EDS analysis diagram of BF_3/nano-sawdust

The amount of boron in the catalyst was determined. For this purpose, a mixture of BF_3/nano-sawdust (0.5 g) and water (50 mL) was stirred and boiled for 1 hour. Then, the mixture was cooled and titrated with 12.5 ml of standard NaOH (0.18 N) in the presence of phenolphetalein. The boron amount in catalyst was found to be 5.5 meq.g-1. In this process, the attached boron in cellulose was reacted with water, captured OH^- from water and produced H^+ that evaluated with OH^- (Scheme 3).



Scheme 3

The thermal gravimetric analysis (TG-DTG) pattern of BF_3/nano-sawdust was detected from 20 to 515 °C (Figure 4). The catalyst is stable until 55 °C and only 15% of its weight was reduced in 115 °C due to the removal of catalyst moisture. Heating the catalyst until 515 °C, caused 73% of its mass to be reduced. The char yield of the catalyst in 515 °C is 30%. According to the TG-DTG diagram of BF_3/nano-sawdust and our study, it was revealed that this catalyst is suitable for the promotion of organic reactions below 115 °C.

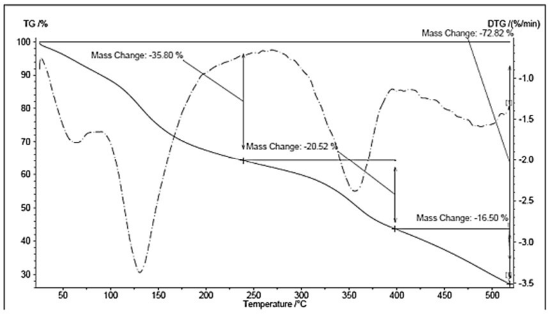
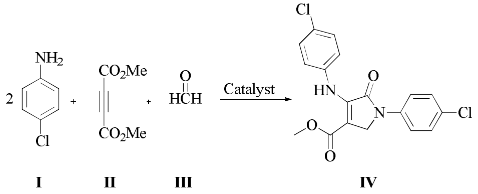


Fig 4: Thermal gravimetric analysis (TG-DTG) pattern of BF_3/nano-sawdust

In this study, we have investigated the catalytic activity of BF_3/nano-sawdust for the synthesis of dihydro-2oxopyrroles via 4CRs of the dialkylacetylenedicarboxylates, amines and aldehyde.

The synthesis of dihydro-2-oxopyrroles is in kind an intermolecular nucleophilic addition reaction (Mannich reaction type) included several intermediates. Therefore, it is necessary the choosing of a suitable conditions such as catalyst, solvent and temperature for this reaction. As a model reaction, synthesis of methyl-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-5-oxo-2,5-dihydro-1H-pyrrole-3 carboxylate was examined under various condition in the presence of BF_3/nano-sawdust as catalyst (Table 1). As shown in table 1, the most yield of reaction was acquired using of 3 mmol of formaldehyde in ethanol at 70 ^oC and in the presence of 0.08 g BF_3/nano-sawdust after 3.5 h (Table 1, Entry 8). Effect of different solvent on the reaction was investigated and revealed that ethanol gave the best results for this transformation. It was be noted when the reaction was performed in the same conditions mentioned in entry 8 without catalyst, desired product was obtained in low yield (Table 1, entry 13). Reusability of catalyst was investigated for three cycles (Table 1, entries 14–16). For this purpose after each run the reaction mixture was diluted with acetone or ethanol and filtered for isolation of catalyst. The obtained catalyst was then washed with chloroform followed by drying in room temperature. The recovered catalyst was then used for the next run of the reactions. It was found that the reactivity of the catalyst decreases marginally for the next run (approx. 3%).

Table1. Preparation of methyl-1(4-chlorophenyl)-4-((4-ethylphenyl)amino)-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate under various conditions.



Entry	Solvent	Catalyst	Reactant I: II:III	Condition	Time	Yield ^{b}
1	EtOH	-	2:1:1.5	R.T.	3h	-
2	EtOH	BF_3/nano-sawdust (0.06)	2:1:1.5	R.T.	3h	14%
3	EtOH	BF_3/nano-sawdust (0.08)	2:1:1.5	R.T.	3h	17%
4	EtOH	BF_3/nano-sawdust (0.08)	2:1:1.5	Reflux	3h	37%
5	EtOH	BF_3/nano-sawdust (0.08)	2:1:2	Reflux	3h	52%
6	EtOH	BF_3/nano-sawdust (0.08)	2:1:2.5	Reflux	3h	62%
7	EtOH	BF_3/nano-sawdust (0.08)	2:1:2.5	Reflux	3.5h	81%
8	EtOH	BF_3/nano-sawdust (0.08)	2:1:3	Reflux	3.5h	92%
9	MeOH	BF_3/nano-sawdust (0.08)	2:1:3	Reflux	3.5h	60%
10	EtOH/MeOH1:1	BF_3/nano-sawdust (0.08)	2:1:3	Reflux	3.5h	67%
11	$CHCl_3$	BF_3/nano-sawdust (0.08)	2:1:3	Reflux	3.5h	24%
12	*n*-Hexane	BF_3/nano-sawdust (0.08)	2:1:3	Reflux	3.5h	38%
13	EtOH	-	2:1:3	Reflux	3.5h	20%
14	EtOH	BF_3/nano-sawdust (0.08), 2nd run	2:1:3	Reflux	3.5h	90%
15	EtOH	BF_3/nano-sawdust (0.08), 3nd run	2:1:3	Reflux	3.5h	87%
16	EtOH	BF_3/nano-sawdust (0.08), 4nd run	2:1:3	Reflux	3.5h	84%
17	MeOH	[*n*-Bu_4N][HSO_4] (10 mol%)	2:1:1	R.T.	4h	86%[26]
18	MeOH	$InCl_3$ (20 mol%)	2:1:1.5^c	R.T.	3h	79%[25]
19	EtOH	AcOH (2 eq)	3:1:1.5^d	Reflux	4h	89%[23]

^{a}Reactions were run with the following steps: (a) dimethylacetylendicarboxylate(1 mmol) and 4-chloroaniline (1 mmol) were added into 4 mL solvent and kept at room temperature for 15 min; (b) 4-chloroaniline (1 mmol), formaldehyde and catalyst were added to the above mixture respectively, and then stirred at rt/ 70 °C for desired time.

^{b}Isolated yield after recrystallization in ethanol.

^{c}Diethylacetylenedicarboxylate instead of dimethylacetylenedicarboxylate was used.

^{d}4-Bromoaniline instead of 4-chloroaniline was used.

Finally, with optimized reaction conditions obtained for the synthesis of IV, from the amount of reactant, solvent, amount of catalyst and reaction temperature point of view, the scope of this transformation was explored. Accordingly, for synthesis of different dihydro-2-oxopyrrole derivatives were examined and high yields were noticed in most of the cases (Table 2)

Experimental section

Materials and methods:
All chemicals and solvents were purchased from the Merck and Fluka Chemical Companies in high purity. Materials were used from the commercial reagent grade. FT-IR spectra were recorded onan attenuated total reflectance-fouriertransform infrared (ATR-FTIR) spectrophotometer (Bruker, Eqinox 55). 1H NMR and 13C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a BrukerDXR-400 spectrometer using $CDCl_3$as solvent and tetramethylsilane as internal standard. Mass spectra (MS) were recorded on a FINNIGAN-MAT 8430 mass spectrometer, operating at an ionization potential of 70 eV. Melting points were obtained with a Buchi melting point B-540 B.V.CHI apparatus. Quantitative elemental information (EDS) of BF_3/nano-sawdust was measured by SEM/EDS instrument, Phenom pro X.

Preparation of nano-sawdust:

Pine sawdust (4 g), was first treated with a solution of 17.5% w/v sodium hydroxide in water bath maintained at 100 °C for 12 hours to remove tannin, pectin, proteins and minerals. The residue was alpha cellulose that is not soluble in 17.5% w/v sodium hydroxide solution. The alkali treated fibers were washed repeatedly. The stock was then bleached with 100ml of 1:1 dilution of 5 % w/v sodium hypochlorite solution at 80 °C for 8 hrs. The resulting was then treated with 10 mlof 20 % v/v hydrogen peroxide at 50°C for 2 hours due to the removal of the insoluble lignin. The resultant was hydrolyzed by refluxing with sulfuric acid (65% H_2SO_4 with fiber to liquor ratio of 1:20) for 2

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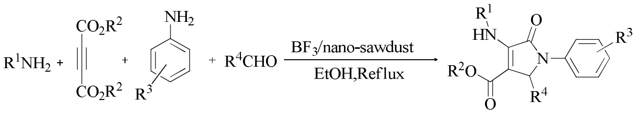
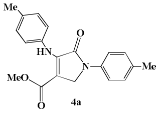
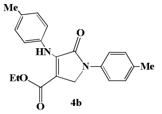
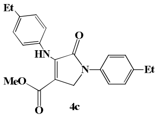
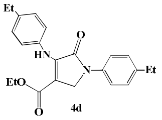
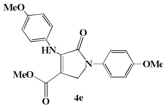
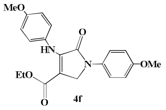
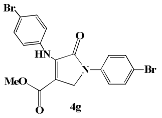
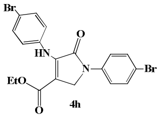
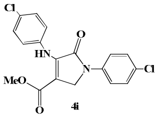
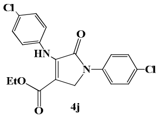
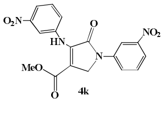
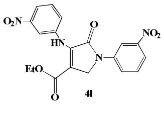
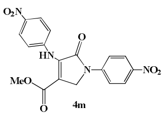
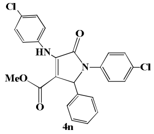
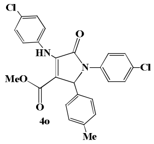
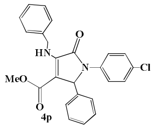
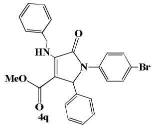
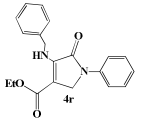
Table 2. Synthesis of dihydro-2-oxopyrrole derivatives in the presence of BF_3/nano-sawdust at 70 °C.[a]



Entry	R^1	R^2	R^3	Product	Time	Yield[b]	M.P. [Ref]
1	4-Me-C_6H_4	Me	4-Me	 4a	4h	84%	175-176[22]
2	4-Me-C_6H_4	Et	4-Me	 4b	4h	88%	128-130[23]
3	4-Et-C_6H_4	Me	4-Et	 4c	4h	81%	125-126[20]
4	4-Et-C_6H_4	Et	4-Et	 4d	4h	80%	98-100
5	4-OMe-C_6H_4	Me	4-OMe	 4e	5h	83%	160-162[20]
6	4-OMe-C_6H_4	Et	4-OMe	 4f	5h	85%	152-154[25]
7	4-Br-C_6H_4	Me	4-Br	 4g	3h	90%	181-182[22]
8	4-Br-C_6H_4	Et	4-Br	 4h	3h	91%	165-166[22]
9	4-Cl-C_6H_4	Me	4-Cl	 4i	3.5h	92%	173-174[22]
10	4-Cl-C_6H_4	Et	4-Cl	 4j	3h	95%	165-167[26]
11	3-NO_2-C_6H_4	Me	3-NO_2	 4k	2h	79%	204-206
12	3-NO_2-C_6H_4	Et	3-NO_2	 4l	2h	85%	191-192
13	4-NO_2-C_6H_4	Et	4-NO_2	 4m	3h	75%	206-208
14	4-Cl-C_6H_4	Me	4-Cl	 4n	3.5h	89%	175 – 177[22]
15	4-Cl-C_6H_4	Me	4-Cl	 4o	4h	92%	148-150[19]
16	$PhCH_2$	Me	4-Cl	 4p	3h	88%	136-138[22]
17	$PhCH_2$	Me	4-Br	 4q	3h	91%	154-156[22]
18	$PhCH_2$	Et	H	 4r	4h	95%	138-140[23]

[a] For entry of 1-13,18 The amount of amine (mmol): dialkylacetylenedicarboxylate (mmol): formaldehyde (mmol): BF_3/nano-sawdust(g) equal to 2:1:3:0.08

for entry of 14-17 The amount of amine (mmol): dialkylacetylenedicarboxylate (mmol): aldehyde (mmol): BF_3/nano-sawdust(g) equal to 2:1:2:0.08

[b] Isolated yields after recrystallization in ethanol.

R^4CHO for entry of 1-13,18was formaldehyde, entry 14,16-17 wasbenzaldehyde and entry 15 was 4-methylbenzaldehyde.

hours at 60 °C with strong agitation. Resulting mixture was cooled to room temperature and diluted by adding an excess of distilled water. Then, the suspension was repeatedly centrifuged at 12000 rpm for 8 minutes using a refrigerated centrifuge (AppendorfCentrifuge 5417R). After each run, the nano-sawdust (as white powder) was washed with distillated water and centrifuged until the supernatant was become neutral.

Preparation of BF_3/nano-sawdust:

In a ventilated room, a 25 mL suction flask equipped with a constant-pressure dropping funnel containing $BF_3.Et_2O$ (1 mL) and gas inlet tube for conducting HF, charged with 1 g nano-sawdust and chloroform, $BF_3.Et_2O$ was added drop wise over a period of 3 min at room temperature. The mixture was stirred for one hour at room temperature. The resulted mixture was filtered. The obtained white solid was washed with chloroform and dried at room temperature.

Typical procedure for synthesis of dihydro-2-oxopyrroles:

In a round-bottom flask (50 mL) equipped with a reflux condenser, firstly, a mixture of substituted amine (1 mmol) and dialkylacetylenedicarboxylate (1 mmol) in absolute ethanol (4 mL) was stirred for 30 min. Then, other substituted amine (1 mmol), formaldehyde 37% (3 mmol) or substituted benzaldehyde (2mmol) and BF_3/nano-sawdust (0.08 g) in absolute ethanol (3

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mL) were added to the above mixture and stirred in 70°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was allowed to be cooled,filtered off and washed with EtOH (3×10 mL) to remove all unreacted substrates.For separation of catalyst from solid product, it was washed with chloroform (15 mL). The chloroform was evaporated and the crude solid product was recrystallized from ethanol to give the corresponding dihydro-2-oxopyrroles.

Conclusions

In summary, BF_3/nano-sawdust as a green, cheap, natural, biodegradable and readily available biopolymer solid acid catalyst introduced. We have shown that various substituted dihydro-2-oxopyrrole derivatives can be successfully synthesis by an operationally simple and high efficient one-pot four-component procedure using BF_3/nano-sawdust. This protocol has many advantages including high conversions, low catalyst loading, low-cost, easy workup and operational simplicity, which makes this method more attractive.

Acknowledgements

The Research Council of Yazd University is gratefully acknowledged for financial support of this study.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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DOI: 10.1039/C4RA16625F

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