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Ethylenediammonium diformate (EDDF) in PEG_{600}: an efficient ambiphilic novel catalytic system for the one-pot synthesis of 4*H*-pyrans *via* Knoevenagel condensation†

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A novel ethylenediammonium diformate–polyethylene glycol (EDDF-PEG_{600}) system was developed as a catalyst for the Knoevenagel condensation and Knoevenagel initiated three-component one-pot synthesis of 4*H*-pyrans at room temperature with high yields and in short reaction times. Further, the EDDF-PEG_{600} catalytic system was recycled six times without any appreciable loss in its activity and hence can be termed as a green, environmentally benign catalytic system. A plausible mechanism depicting the ambiphilic nature of EDDF (catalyst) and PEG (promoting medium) acting in synergy has been proposed.

Introduction

In the context of green chemistry and due to increasing regulatory and economic pressures, there is always a need for generating catalytic systems and processes that are environmentally benign, have high atom-economies and are high-yielding.[1] Many recent discoveries in the field of synthetic organic chemistry are centred on these issues and these are ever-increasing. One such finding is the effect of ionic environment on the outcome of a reaction as exemplified by the use of ionic liquids (ILs, weakly co-ordinated salts).[2] ILs have found numerous applications, the most prominent being their use as alternate reaction media and as catalysts for important organic transformations.[2] Recently, it has been proposed that the cation and anion of an IL may act cooperatively as nucleophilic and electrophilic catalysts (ambiphilic dual activation) thereby catalysing various organic reactions more efficiently.[3] However, there are still some issues associated with the use of ionic liquids such as toxicity, biodegradability and many of the processes to produce ILs are themselves not green.[4,5] Hence, it would be beneficial to combine the best of ionic catalysis and the use of greener environmentally-friendly solvents.

Ethylenediammonium diacetate (EDDA), a salt (m.p. 120 °C), has been reported as an efficient catalyst for limited organic reactions such as Knoevenagel condensations, intramolecular hetero-Diels–Alder and some domino reactions.[6] We thought that replacement of the acetate counterion of EDDA by the formate ion might improve the acidic nature and also the catalytic activity of the resulting ethylenediammonium diformate (EDDF). EDDF is a salt (m.p. 132 °C), and was reported as a precursor for the synthesis of various mono- and di-N-substituted ethylenediamines in 1954.[7] To the best of our knowledge there are no scientific reports on its catalytic activity. Encouraged by recent reports on the catalytic potential of ammonium based salts such as EDDA,[6] 2-hydroxyethylammonium formate (HEAF),[8,9] together with the concept of ambiphilic dual activation,[3,9,10] and as a part of our ongoing work towards the synthesis of biologically relevant molecules,[11] we explored EDDF's catalytic potential and report herein EDDF-PEG_{600} as an efficient novel catalytic system for the Knoevenagel condensation and subsequent one-pot synthesis of various 4*H*-pyrans.

Pyrans are important heterocycles found in various natural products and many compounds possessing the 4*H*-pyran ring system, including chromenes and spirooxindoles, have shown a wide range of biological activities.[12–14] 4*H*-Pyrans are synthesised easily through a one-pot domino Knoevenagel–Michael–Thorpe–Ziegler reaction sequence,[15] which is a Knoevenagel initiated domino reaction. Recently many green approaches for the Knoevenagel reaction have been reported using catalysts such as ionic liquids ([bmim]OH, [MMIm][MSO_4]), enzymes (BLAP, baker's yeast), clays and heterogeneous catalysts *etc*.[16-18] However, these methods still pose problems such as long reaction times, low yields, tedious work-ups, expensive catalysts, recyclability issues, and some processes may not be feasible from an industrial point of view. To this end, we studied a model Knoevenagel reaction between benzaldehyde and malononitrile and tested EDDF for its

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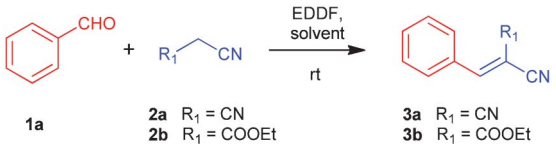
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of EDDF, 4*H*-pyrans **7i**, **7u**, **7v**, **8a**, **9a** and spirooxindoles **11a**, **12a**, **13a**. See DOI: 10.1039/c3ra42410c



Scheme 1 EDDF catalysed Knoevenagel condensation of benzaldehyde (**1a**) with malononitrile/ethyl cyanoacetate (**2a** or **2b**).

catalytic activity. Based on our initial results, EDDF was dispersed in PEG_{600} by ultrasonication and then examined as a novel catalytic system for synthesizing an array of 4*H*-pyrans *via* Knoevenagel-initiated domino reactions.

Results and discussion

The initial studies were carried out on the model Knoevenagel condensation of benzaldehyde with malononitrile using 20 mol% EDDF as catalyst with various solvents at ambient temperature (Scheme 1, Table 1). Good yields (79–86%) were obtained in almost all polar solvents and with the combination of PEG the reaction completed within a minute and furnished more than 90% isolated yield (Table 1, entries 6 and 7). The efficacy of the catalytic system was also studied with ethyl cyanoacetate as active methylene substrate.

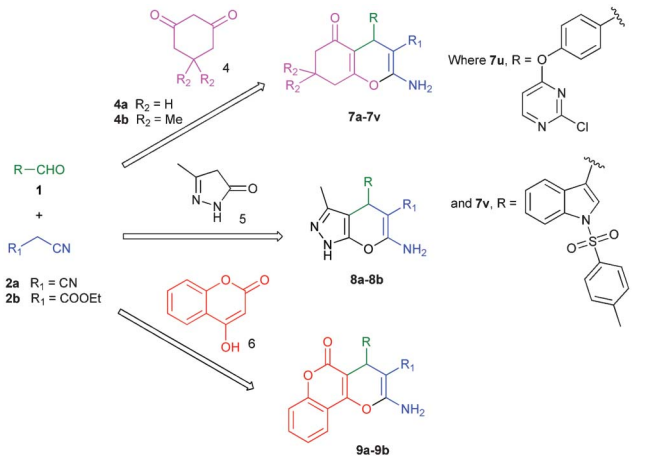
Next, the amount of EDDF was decreased and it was observed that 5 mol% of EDDF in PEG_{600} would suffice. PEG_{600} was preferred over PEG_{400} since the latter is more hygroscopic[19] and the higher weight PEGs are solids. The model reaction was also performed in either PEG_{600} or EDDF, but the progress of the reaction was slow (Table 1, entries 9 and 10). Thus, it was concluded that the combination of EDDF and PEG_{600} was the best catalytic system for the Knoevenagel condensation.

With these initial encouraging results in hand, we wished to develop a catalytic system involving EDDF (catalyst) and

Table 1 Optimisation conditions for EDDF catalysed Knoevenagel condensation reaction in various solvents at room temperature[a]

Entry	R	Catalyst (mol%)	Solvent	Time [min]	Yield [%][b]
1	CN	EDDF (20)	MeOH	2	81
2	CN	EDDF (20)	Toluene	60	50
3	CN	EDDF (20)	EtOH	2	86
4	CN	EDDF (20)	ACN	2	80
5	CN	EDDF (20)	H_2O	2	79
6	CN	EDDF (20)	PEG_{400}	1	92
7	CN	EDDF (20)	PEG_{600}	1	96
8	COOEt	EDDF (20)	PEG_{600}	25	87
9	CN	—	PEG_{600}	15	82
10	CN	EDDF (20)	—	2	70
11	CN	EDDF (10)	PEG_{600}	1	95
12	CN	EDDF (5)	PEG_{600}	1	95
13	CN	EDDF (1)	PEG_{600}	4	81

[a] Benzaldehyde **1a** (1 mmol), malononitrile/ethyl cyanoacetate **2** (1 mmol), EDDF (1–20 mol%), solvent (0.5 mL). [b] Isolated yield.



Scheme 2 Synthesis of 4*H*-pyran derivatives.

PEG_{600} (promoting medium/solvent) that is easy to handle and also recyclable. For this purpose, an EDDF-PEG_{600} system was prepared by dispersing EDDF (150 mg) in 10 mL of PEG_{600} by ultrasonic irradiation for 7 h. This catalytic system was subsequently applied for the synthesis of various 4*H*-pyrans *via* a one-pot three-component reaction. First, we performed the one-pot reaction between various aromatic/aliphatic aldehydes, malononitrile/ethyl cyanoacetate and dimedone/1,3-cyclohexadione with the EDDF-PEG_{600} catalytic system at ambient temperature to form 4*H*-pyrans (Scheme 2). All the reactions with malononitrile showed good to excellent yields in relatively short reaction times without any side reactions (Table 2). The work-up procedure was quite simple and involved addition of a small amount of water to afford the product as a precipitate which was filtered and dried under vacuum. When ethyl cyanoacetate was used (Table 2, entry **7b**), the progress of the reaction was slow and furnished moderate yield even after 30 min, which was attributed to the competing formation of the Knoevenagel adduct of benzaldehyde with the 1,3-dicarbonyl owing to the strong catalytic activity of the EDDF-PEG_{600} system. Aromatic aldehydes with electron withdrawing substituents (NO_2, CF_3, F, Cl, Br) at *ortho*, *para* and *meta* positions showed the best reactivity with 85–98% yields. Whereas, aromatic aldehydes with electron donating substituents (*p*-methoxy, *p*-methyl) and aliphatic aldehydes showed less reactivity with moderate to good yields (65–75%) (Table 2, entries **7g**, **7h**, **7n** and **7o**). To study the versatility of the EDDF-PEG_{600} catalytic system, the reaction was performed by replacing dimedone/1,3-cyclohexadione with other carbonyl compounds possessing reactive an α-methylene group such as pyrazolone (**5**) and 4-hydroxycoumarin (**6**) to yield the dihydropyrano[2,3-*c*]pyrazoles (**8a**, **8b**) and dihydropyrano[2,3-*c*]chromenes (**9a**, **9b**) (Scheme 2).

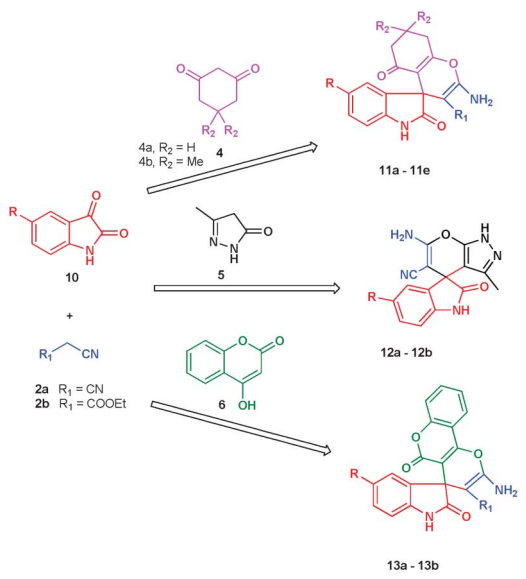
Next, in order to further examine the efficacy of the catalytic system, aldehydes were replaced with isatins to form diverse spirooxindole derivatives *via* the one-pot reaction of isatin, malononitrile/ethyl cyanoacetate and various carbonyl substrates with an active α-methylene group (1,3-cyclohexadione/

Table 2 EDDF-PEG_{600} catalysed one-pot three-component synthesis of various 4*H*-pyrans *via* Knoevenagel reaction at room temperature[a]

Entry	Sub.	R	R_1	Time [min]	Yield [%][b]	m.p. [°C] Observed	m.p. [°C] Literature
7a	**4a**	Ph	CN	5	89	230–231	[229–231][20]
7b	**4a**	Ph	COOEt	40	63	181–183	[180–181][24]
7c	**4a**	4-Br-Ph	CN	8	92	224–226	[220–224][26]
7d	**4a**	4-Cl-Ph	CN	8	89	226–228	[225–227][20]
7e	**4a**	4-F-Ph	CN	7	88	221–223	Unknown
7f	**4a**	4-NO_2-Ph	CN	16	88	233–235	[235–237][20]
7g	**4a**	4-Me-Ph	CN	11	75	215–217	[216–218][23]
7h	**4a**	4-OMe-Ph	CN	13	70	193–194	[190–192][20]
7i	**4a**	4-CF_3-Ph	CN	7	91	210–212	Unknown
7j	**4a**	3-F-Ph	CN	8	85	236–238	Unknown
7k	**4a**	2-F-Ph	CN	5	87	242–244	Unknown
7l	**4a**	3-NO_2-Ph	CN	7	94	204–207	[201–203][20]
7m	**4a**	2-NO_2-Ph	CN	5	98	198–200	[196–198][21]
7n	**4a**	Cyclohexyl	CN	20	65	208–210	Unknown
7o	**4a**	Propyl	CN	25	72	190–192	[188–190][21]
7p	**4b**	Ph	CN	6	61	223–225	[224–225][21]
7q	**4b**	4-Br-Ph	CN	6	89	205–207	[203–205][25]
7r	**4b**	2-NO_2-Ph	CN	7	91	226–227	[224–226][21]
7s	**4a**	2,4-Cl-Ph	CN	7	86	218–220	[221–223][20]
7t	**4a**	3,5-F-Ph	CN	8	96	250–252	Unknown
7u	**4a**	[c]	CN	8	87	236–238	Unknown
7v	**4a**	[c]	CN	25	88	234–236	Unknown
8a	**5**	Ph	CN	10	89	246–247	[244][22]
8b	**5**	2-NO_2-Ph	CN	9	93	240–242	[241][22]
9a	**6**	Ph	CN	12	91	257–259	[256–258][27]
9b	**6**	3-NO_2-Ph	CN	9	88	260–262	[262–264][27]

[a] Aldehyde **1** (1 mmol), malononitrile or ethyl cyanoacetate **2** (1 mmol), compound **4**, **5** or **6** (1 mmol), EDDF-PEG_{600} (0.5 mL). [b] Isolated yield. [c] For **7u** and **7v** the aldehydes used were 4-((2-chloropyrimidin-4-yl)oxy)benzaldehyde and 1-tosyl-1*H*-indole-3-carbaldehyde respectively (Scheme 2).

dimedone or pyrazolone or 4-hydroxycoumarin) (Scheme 3). The reactions proceeded smoothly and gave high yields in short reaction times at room temperature (Table 3). The yield



Scheme 3 Synthesis of spirooxindole derivatives.

Table 3 EDDF-PEG_{600} catalysed one-pot synthesis of various spirooxindoles at room temperature[a]

Entry	Sub.	R	R_1	Time [min]	Yield [%][b]	m.p. [°C] Observed	m.p. [°C] Literature
11a	**4a**	H	CN	7	87	300–301	[298–299][28]
11b	**4b**	H	CN	12	91	293–295	[290–292][28]
11c	**4a**	Br	CN	7	79	292–294	[290–292][28]
11d	**4b**	Br	CN	9	87	>300	[>300][28]
11e	**4a**	H	COOEt	60	59	252–254	[253–255][28]
12a	**5**	H	CN	5	87	284–286	[285–286][29]
12b	**5**	Br	CN	6	83	290–292	[282–283][29]
13a	**6**	H	CN	12	89	>300	[>300][28]
13b	**6**	Br	CN	11	92	>300	[>300][28]

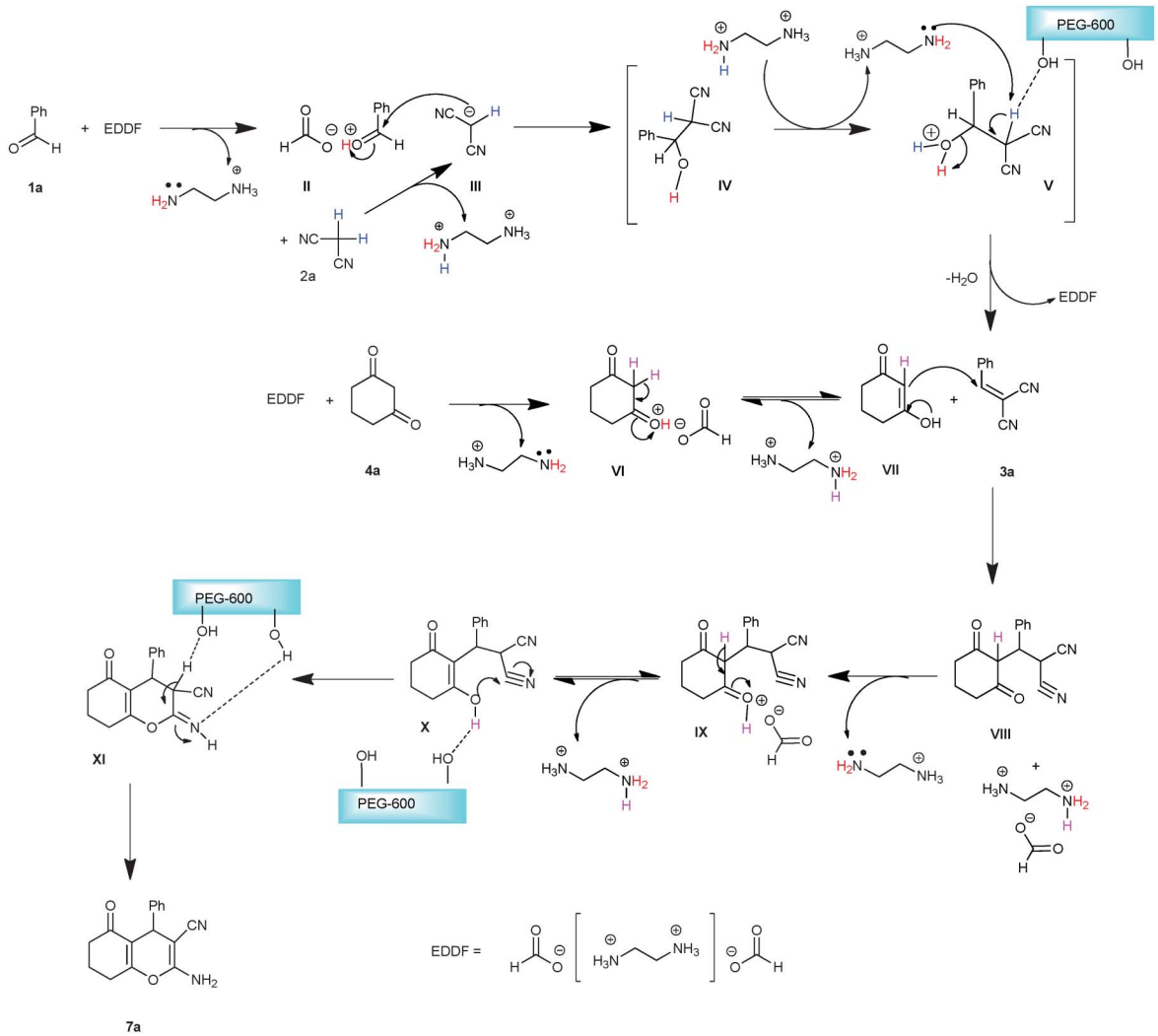
[a] Isatin **10** (1 mmol), malononitrile or ethyl cyanoacetate **2** (1 mmol), compound **4**, **5** or **6** (1 mmol), EDDF-PEG_{600} (0.5 mL). [b] Isolated yield.

with ethyl cyanoacetate was not so encouraging due to the aforementioned reason, but all the reactions with malononitrile gave high yields.

Scheme 4 depicts a plausible mechanism for the EDDF-PEG_{600} catalysed one-pot synthesis of 4*H*-pyrans. Probably, the ethylenediammonium part (acidic) induces the electrophilicity of the carbonyl group *via* protonation and hence aids in the attack of malonate carbanion **III**. A similar mechanism showing the ambiphilic dual activation role of HEAF in the Henry reaction has been reported.[9] The resulting intermediate **V** is stabilised by PEG_{600} *via* H-bonding and EDDF acts as an ambiphile in the rest of the steps to form Knoevenagel product **3a**. On the other hand, the role of EDDF in aiding keto–enol tautomerism in the dicarbonyl (**4a** to **VII**) is also envisioned, which undergoes Michael-addition with the Knoevenagel product **3a** to give intermediate **VIII**, which is protonated (**IX**) followed by tautomerisation to give intermediate **X** (assisted again by EDDF) and finally undergoes cyclisation and imine–amine tautomerism to yield the 4*H*-pyran **7a**. PEG_{600} plays a significant role as a polarizing and stabilizing medium in the overall sequence of the mechanism (intermediates **V**, **X** and **XI**) and acts synergistically. Hence, by using such a hybrid catalytic system that includes the catalyst and the promoter, better catalytic activity can be anticipated.

The reusability of the EDDF-PEG_{600} catalytic system was also examined on a model one-pot reaction between benzaldehyde, malononitrile and 1,3-cyclohexadione under the optimised conditions (Table 2, entry **7a**). After completion of the reaction, water was added and the resultant solid product was filtered, washed with water and the combined filtrate containing the catalyst was concentrated under reduced pressure to remove water. The recovered EDDF-PEG_{600} was re-used at least six times without any appreciable loss in its catalytic activity (Fig. 1).

The FT-IR spectrum of EDDF was recorded before and after dispersion in PEG_{600} (Fig. 2a and 2c). The broad band with weak intensity in the range of 3400–2350 cm^{-1} exhibits a characteristic ammonium structure and the band at 1600



Scheme 4 Plausible mechanism of the EDDF-PEG_{600} catalysed one-pot three-component synthesis of 4*H*-pyran **7a**.

cm^{-1} represents the carbonyl stretching (formate) and N–H plane bending vibrations of the ammonium ion (Fig. 2a).[30] After dispersion of EDDF in PEG_{600}, the broad band appearing at ~3400 cm^{-1} indicated that the ammonium of EDDF is embedded with the O–H stretching vibration of PEG_{600} with absorbed moisture and the band appearing at 2935 cm^{-1} indicates the C–H stretching of the ethylene groups of both EDDF and PEG as shown in Fig. 2c. The IR spectrum of EDDF-PEG_{600} was recorded after six cycles for the synthesis of 4*H*-pyran (**7a**) and no appreciable changes were observed (Fig. 2d). Further, to check the applicability of the developed catalytic system at large scales, model reactions between different substrates were performed at the 100 mmol scale and the results are summarised in Table 4.

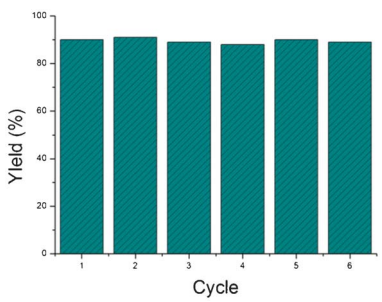


Fig. 1 Comparative recycling study of the EDDF-PEG_{600} catalyst for the synthesis of 4*H*-pyran (**7a**).

Experimental

All reagents were purchased from Merck and Aldrich and were used as such. Reaction progress was monitored using pre-coated TLC plates (E. Merck Kieselgel 60 F254) and spots were visualised under UV light and also by exposing TLC plates to iodine vapour. ^{1}H NMR and ^{13}C NMR spectra were taken on a Jeol Spectrospin spectrometer at 400 MHz and 100 MHz respectively using TMS as an internal standard. Melting points

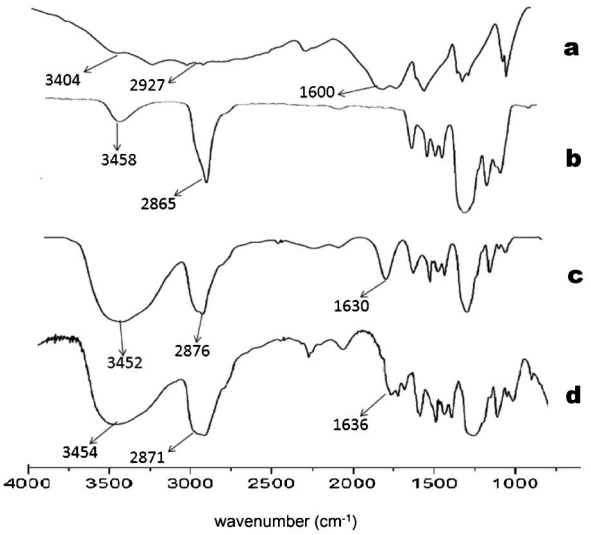


Fig. 2 FT-IR spectra of (a) EDDF, (b) PEG_{600}, (c) fresh EDDF-PEG_{600} and (d) sixth time recycled EDDF-PEG_{600}.

were recorded in open capillary tubes on an ERS automated melting point apparatus and are uncorrected. IR spectra were recorded using Perkin-Elmer and Bruker FT-IR in the range of 4000–100 cm^{-1} and only characteristic frequencies are expressed.

Preparation and characterisation of the catalyst

Procedure for the preparation of EDDF. Ethylenediamine (10 mL, 0.15 mol) was diluted with 15 mL of acetone and was added dropwise to a previously cooled and stirred mixture of 90% formic acid (aq.) (12.5 mL, 0.30 mol) and 15 mL of acetone. The reaction mixture was maintained at 0 °C under continuous stirring for 2 h. The precipitated ethylenediammonium diformate (EDDF) as a white solid was filtered, washed with acetone and dried at 50 °C under vacuum. Yield: 98%; mp 130–132 °C (Lit 132 °C);[7] IR (ν_{max}/cm^{-1}, KBr): 3410, 3162, 2927, 2817, 2121, 1600, 1511, 1375, 1095, 1062, 789, 765; ^{1}H NMR (400 MHz, DMSO): δ_H 2.82 (s, 4H), 8.37 (s, 2H); ^{13}C NMR (100 MHz, D_2O): δ_C 37.64, 171.07.

Procedure for the preparation of EDDF-PEG_{600}. EDDDF-PEG_{600} was prepared by dispersing 150 mg of EDDF in 10 mL of PEG_{600} using ultrasonic irradiation for 7 h. The resulting homogeneous and well dispersed mixture was collected and characterised by IR.

Table 4 Comparison of the EDDF-PEG_{600} catalysed one-pot synthesis of 4*H*-pyrans and spirooxindoles on 1 mmol and 100 mmol reaction scales

	1 mmol scale[b]		100 mmol scale	
Entry	Time [min]	Yield [%][a]	Time [min]	Yield [%][a]
7a	5	89	6	94
8a	10	89	11	92
9a	12	91	13	95
11a	7	87	7	94
12a	5	87	5	93
13a	12	89	13	95

[a] Isolated yield. [b] From Table 2 and Table 3.

Procedure for Knoevenagel condensation reaction

A mixture of benzaldehyde (1 mmol), malononitrile/ethyl cyanoacetate (1 mmol) and EDDF (1–20 mol%) in appropriate solvent (0.5 mL) was stirred for an appropriate time at room temperature. After completion of reaction as monitored by TLC, water (2 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was evaporated under reduced pressure and the resulting solid was recrystallised from ethanol to give pure product.

General procedure for the synthesis of 4*H*-pyrans

To a mixture of aldehyde **1** (1 mmol), malononitrile or ethyl cyanoacetate **2a** or **2b** (1 mmol), and carbonyl compound possessing a reactive α-methylene group **4**, **5** or **6** (1 mmol) was added 0.5 mL of EDDF-PEG_{600} and the mixture was stirred at room temperature for the respective time as mentioned in Table 2. After completion of the reaction (monitored by TLC), water (5 mL) was added and the resulting precipitate was filtered, washed with water (20 mL) and recrystallised from ethanol. The filtrate containing catalyst was extracted with diethyl ether (3 × 5 mL), the aqueous layer was separated and water was evaporated under reduced pressure at 50 °C to give pure catalyst which can be used for the next run under the same conditions.

General procedure for the synthesis of spirooxindoles

To a mixture of isatin **10** (1 mmol), malononitrile or ethyl cyanoacetate **2a** or **2b** (1 mmol), and carbonyl compound possessing a reactive α-methylene group **4**, **5** or **6** (1 mmol) was added 0.5 mL of EDDF-PEG_{600} and the mixture was stirred at room temperature for the respective time as mentioned in Table 3. After completion of the reaction (monitored by TLC), water (5 mL) was added and the resulting precipitate was filtered, washed with water followed by cold ethanol and dried under vacuum at 50 °C resulting in the desired product.

Spectral data of selected compounds

2-Amino-5-oxo-4-(4-trifluoromethylphenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (7i). White solid, mp 210–212 °C; IR (ν_{max}/cm^{-1}, KBr): 3430, 3335, 2972, 2197, 1682, 1659, 1597, 1422, 1365, 1260, 1161, 1105, 1004, 846, 509; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ_H 1.88–1.97 (m, 2H), 2.24–2.31 (m, 2H), 2.58–2.67 (m, 2H), 4.29 (s, 1H), 7.10 (br s, 2H), 7.38 (d, 2H, J = 8.05 Hz), 7.64 (d, 2H, J = 8.05 Hz); ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si): δ_C 19.74, 26.48, 35.50, 36.23, 57.31, 113.02, 119.40, 122.91, 125.31, 127.24, 128.07, 149.35, 158.49, 164.93, 195.90; ESI-MS (m/z): 335.13 $(M + H)^+$; Anal. Calcd for $C_{17}H_{13}F_3N_2O_2$: C, 61.08; H, 3.92; N, 8.38; found: C, 61.13; H, 3.90; N, 8.41%.

2-Amino-4-(3,5-difluorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (7t). White solid, mp 250–252 °C; IR (ν_{max}/cm^{-1}, KBr): 3335, 3327, 3179, 2927, 2192, 1684, 1647, 1459, 1369, 1216, 1119, 1003, 859, 696; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ_H 1.82–1.85 (m, 2H), 2.17–2.21 (m, 2H), 2.41–2.61 (m, 2H), 4.16 (s, 1H), 6.78 (dd, 2H, J = 2.2 Hz, J = 8.79 Hz), 6.93–6.96 (m, 1H), 7.02 (br s, 2H); ^{13}C NMR (100 MHz; $CDCl_3$;

Me_4Si): δ_C 19.73, 26.55, 35.31, 36.27, 57.11, 102.15, 110.46, 112.53, 119.46, 149.55, 158.55, 161.13, 163.58, 165.35, 196.05; ESI-MS (*m*/*z*): 303.10 $(M + H)^+$; Anal. Calcd for $C_{16}H_{12}F_2N_2O_2$: C, 63.57; H, 4.00; N, 9.27; found: C, 63.67; H, 4.04; N, 9.25%.

2-Amino-4-[4-(2-chloropyrimidin-4-yloxy)phenyl]-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (7u). White solid, mp 236–238 °C; IR (ν_{max}/cm^{-1}, KBr): 3337, 3321, 3183, 2922, 2189, 1677, 1646, 1607, 1562, 1458, 1332, 1191, 953, 844, 532; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ_H 1.88–1.98 (m, 2H), 2.24–2.38 (m, 2H), 2.58–2.68 (m, 2H), 4.25 (s, 1H), 7.05 (br s, 2H), 7.11 (d, 1H, *J* = 5.13 Hz), 7.18 (d, 2H, *J* = 8.05 Hz), 7.25 (d, 2H, *J* = 8.05 Hz), 8.60 (d, 1H, *J* = 5.13 Hz); ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si): δ_C 19.77, 26.51, 34.91, 36.31, 57.96, 107.64, 113.60, 119.77, 121.26, 128.65, 142.66, 150.12, 158.59, 159.00, 161.47, 164.81, 169.99, 196.02; ESI-MS (*m*/*z*): 395.09 $(M + H)^+$, 396.09 $(M + 2)^+$; Anal. Calcd for $C_{20}H_{15}ClN_4O_3$: C, 60.84; H, 3.83; N, 14.19; found: C, 60.81; H, 3.85; N, 14.20%.

2-Amino-5-oxo-4-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (7v). White solid, mp 234–236 °C; IR (ν_{max}/cm^{-1}, KBr): 3435, 3422, 3198, 2944, 2194, 1678, 1655, 1364, 1173, 975, 740, 674, 568; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ_H 1.69–1.71 (m, 1H), 1.79–1.85 (m, 1H), 2.07–2.24 (m, 5H), 2.42–2.59 (m, 2H), 4.43 (s, 1H), 6.94 (br s, 2H), 7.09–7.12 (m, 1H), 7.15–7.17 (m, 1H), 7.19–7.22 (m, 2H), 7.29–7.31 (m, 1H), 7.47 (s, 1H), 7.65 (d, 2H, *J* = 8.05 Hz), 7.73 (d, 1H, *J* = 8.05 Hz); ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si): δ_C 19.86, 21.00, 26.48, 27.08, 36.29, 56.52, 112.05, 113.44, 119.57, 119.65, 123.39, 124.39, 124.59, 125.27, 126.59, 128.88, 130.13, 134.01, 134.83, 145.31, 158.73, 164.72, 195.83; ESI-MS (*m*/*z*): 460.09 $(M + H)^+$; Anal. Calcd for $C_{25}H_{21}N_3O_4S$: C, 65.34; H, 4.61; N, 9.14; S, 6.98; found: C, 65.37; H, 4.65; N, 9.12; S, 6.95%.

6-Amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (8a). White solid; mp 246–247 °C; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ_H 1.76 (s, 3H, CH_3), 4.58 (s, 1H), 6.86 (br s, 2H, NH_2), 7.15 (d, 2H, *J* = 7.32 Hz), 7.19–7.22 (m, 1H), 7.28–7.32 (m, 2H), 12.08 (s, 1H, NH); ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si): δ_C 9.7, 36.22, 57.16, 97.64, 120.82, 126.73, 127.46, 128.43, 135.57, 144.44, 154.76, 160.86.

2-Amino-5-oxo-4-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (9a). White solid, mp 257–259 °C; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si) δ_H 4.40 (s, 1H), 7.19–7.21 (m, 3H), 7.25–7.29 (m, 2H), 7.36 (br s, 2H, NH_2), 7.39–7.48 (m, 2H), 7.66 (t, 1H, *J* = 7.25 Hz), 7.86 (d, 1H, *J* = 8.05 Hz).

2-Amino-2′,5-dioxo-5,7-dihydrospiro[furo[3,4-*b*]pyran-4,3′-indoline]-3-carbonitrile (11a). Off-white solid; mp 300–301 °C; IR (ν_{max}/cm^{-1}, KBr): 3375, 3287, 3136, 2190, 1713, 1682, 1650, 1602, 1469, 1355, 1210, 1078, 1009; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si) δ_H 1.85–1.96 (m, 2H), 2.15–2.28 (m, 2H), 2.64 (t, 2H, *J* = 5.86 Hz), 6.76 (d, 1H, *J* = 8.05 Hz), 6.84–6.91 (m, 1H), 6.98 (d, 1H, *J* = 7.32 Hz), 7.10–7.15 (m, 1H), 7.20 (bs s, 2H), 10.37 (bs s, 1H); ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si): δ_C 19.81, 26.76, 36.40, 46.89, 57.54, 109.16, 111.88, 117.38, 121.66, 123.21, 128.16, 134.55, 142.00, 158.66, 166.80, 178.17, 195.05; ESI-MS (*m*/*z*): 308.11 $(M + H)^+$; Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67; found: C, 66.47; H, 4.28; N, 13.68%.

6′-Amino-3′-methyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (12a). Off-white solid, mp 284–286 °C; IR (ν_{max}/cm^{-1}, KBr): 3421, 3389, 3339, 3138, 2685, 2184, 1711, 1650, 1582, 1516, 1411, 1322, 1209, 1157, 1053, 933, 698; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ_H 1.51 (s, 3H), 6.89 (d, 1H, *J* = 8.05 Hz), 6.95–7.07 (m, 2H), 7.17–7.27 (m, 3H), 10.58 (br s, 1H), 12.27 (br s, 1H, NH); ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si): δ_C 9.00, 47.33, 55.20, 95.43, 109.73, 118.79, 122.57, 124.56, 128.96, 132.71, 134.78, 141.54, 155.30, 162.52, 178.08; ESI-MS (*m*/*z*): 294.11 $(M + H)^+$; Anal. Calcd for $C_{15}H_{11}N_5O_2$: C, 61.43; H, 3.78; N, 23.88; found: C, 61.46; H, 3.75; N, 23.91%.

2′-Amino-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile (13a). Off-white solid, mp >300 °C; IR (ν_{max}/cm^{-1}, KBr): 3475, 3356, 3119, 2197, 1736, 1679, 1623, 1474, 1365, 1073; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ_H 6.84 (d, 1H, *J* = 7.32 Hz), 6.91–6.94 (m, 1H), 7.20 (d, 2H, *J* = 7.32 Hz), 7.48 (d, 1H, *J* = 8.05 Hz), 7.51–7.55 (m, 1H), 7.65 (s, 2H), 7.74–7.78 (m, 1H), 7.93 (dd, 1H, *J* = 1.46 Hz, *J* = 7.32 Hz), 10.66 (br s, 1H); ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si): δ_C 47.60, 57.03, 101.43, 109.52, 112.37, 116.68, 116.97, 122.07, 122.68, 124.13, 125.03, 128.93, 133.03, 133.69, 142.19, 152.03, 155.07, 158.27, 158.45, 177.13; ESI-MS (*m*/*z*): 358.09 $(M + H)^+$; Anal. Calcd for $C_{20}H_{11}N_3O_4$: C, 67.23; H, 3.10; N, 11.76; found: C, 67.21; H, 3.15; N, 11.79%.

Conclusions

To conclude, a highly efficient catalytic system combining EDDF (catalyst) and PEG_{600} (promoting medium) was developed for the first time and applied as a novel catalyst for the Knoevenagel condensation and Knoevenagel initiated one-pot synthesis of various 4*H*-pyrans including chromenes and spirooxindoles. EDDF can act as a cooperative ambiphilic catalyst in the reaction sequence, while PEG may provide a polarising medium and assist in stabilising the reaction intermediates. The developed catalytic system was easy to handle, green, non-toxic, inexpensive and gave high yields at shorter reaction times. The main advantage of the EDDF-PEG_{600} catalytic system was that the reactions could be performed at room temperature and showed excellent tolerance towards a wide range of substrates. Further, it was recycled and showed no appreciable loss in reaction yields. Moreover, owing to its simplicity and amenability to large scale operation, it can be termed as a useful and effective way to synthesise such an important class of compounds. Further investigation into the ability of the EDDF-PEG_{600} system to catalyse a number of reactions of synthetic importance is underway.

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Notes and references

1 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998.
2 (*a*) T. Fischer, A. Sethi, T. Welton and J. Woolf, *Tetrahedron Lett.*, 1999, **40**, 793; (*b*) S. Keskin, D. K. Talay, U. Akman and O. Hortacsu, *J. Supercrit. Fluids*, 2007, **43**, 150; (*c*) T. Welton, *Chem. Rev.*, 1999, **99**, 2071.
3 (*a*) V. Lucchini, M. Noe, M. Selva, M. Fabris and A. Perosa, *Chem. Commun.*, 2012, **48**, 5178; (*b*) A. K. Chakraborti and S. R. Roy, *J. Am. Chem. Soc.*, 2009, **131**, 6902; (*c*) A. Zhu, R. Liu, L. Lingjun, L. Liangyun, W. Lan and W. Jianji, *Catal. Today*, 2013, **200**, 17.
4 T. Welton, *Green Chem.*, 2011, **13**, 225.
5 W. M. Nelson, *ACS Symp. Ser.*, 2002, **818**, 30.
6 (*a*) S. Majumder and P. J. Bhuyan, *Tetrahedron Lett.*, 2012, **53**, 137; (*b*) K. S. Rao and Y. R. Lee, *Tetrahedron*, 2012, **68**, 226; (*c*) Y. R. Lee and T. V. Hung, *Tetrahedron*, 2008, **64**, 7338; (*d*) C. Su, Z. C. Chen and Q. G. Zheng, *Synthesis*, 2003, 555.
7 J. L. Szabo, S. V. Lieberman and W. F. Bruce, *Br. Pat.* GB716598, 1954.
8 (*a*) A. Ying, H. Liang, R. Zheng, C. Ge, H. Jiang and C. Wu, *Res. Chem. Intermed.*, 2011, **37**, 579; (*b*) H. R. Shaterian, M. Arman and F. Rigi, *J. Mol. Liq.*, 2011, **158**, 145; (*c*) A. Alizadeh, M. M. Khodaei and A. Eshghi, *Can. J. Chem.*, 2010, **88**, 514; (*d*) Y. O. Sharma and M. S. Degani, *J. Mol. Catal. A: Chem.*, 2007, **277**, 215.
9 A. Alizadeh, M. M. Khodaei and A. Eshghi, *J. Org. Chem.*, 2010, **75**, 8295.
10 D. Kumar, D. N. Kommi, P. Chopra, M. I. Ansari and A. K. Chakraborti, *Eur. J. Org. Chem.*, 2012, 6407.
11 (*a*) K. Arya, D. S. Rawat and H. Sasai, *Green Chem.*, 2012, **14**, 1956; (*b*) K. Arya, U. C. Rajesh and D. S. Rawat, *Green Chem.*, 2012, **14**, 3344; (*c*) M. Sharma, S. Manohar and D. S. Rawat, *J. Heterocycl. Chem.*, 2012, **49**, 589; (*d*) S. Manohar, U. C. Rajesh, S. I. Khan, B. L. Tekwani and D. S. Rawat, *ACS Med. Chem. Lett.*, 2012, **3**, 555; (*e*) R. Mamgain, R. Singh and D. S. Rawat, *J. Heterocycl. Chem.*, 2009, **46**, 69; (*f*) H. Atheaya, S. I. Khan, R. Mamgain and D. S. Rawat, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1446; (*g*) G. S. Bisht, D. S. Rawat, A. Kumar, R. Kumar and S. Pasha, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4343; (*h*) A. J. Krzysiak, D. S. Rawat, S. A. Scott, J. E. Pais, M. Handley, M. L. Harrison, C. A. Fierke and R. A. Gibbs, *ACS Chem. Biol.*, 2007, **2**, 385; (*i*) M. C. Joshi, G. S. Bisht and D. S. Rawat, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3226; (*j*) Beena, N. Kumar, R. K. Rohilla, N. Roy and D. S. Rawat, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1396; (*k*) N. Kumar, S. I. Khan, M. Sharma, H. Atheaya and D. S. Rawat, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1675.
12 K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134.
13 (*a*) Y. Tang, J. Oppenheimer, Z. Song, L. You, X. Zhang and R. P. Hsung, *Tetrahedron*, 2006, **62**, 10785; (*b*) T. C. M. Kee, R. W. Fuller, C. D. Covington, J. H. Cardellina, R. J. Gulakowski, B. L. Krepps, J. B. M. Mahon and M. R. Boyd, *J. Nat. Prod.*, 1996, **59**, 754; (*c*) T. C. McKee, C. D. Covington, R. W. Fuller, H. R. Bokesch, S. Young, J. H. Cardellina, M. R. Kadushin, D. D. Soejarto, P. F. Stevens, G. M. Cragg and M. R. Boyd, *J. Nat. Prod.*, 1998, **61**, 1252; (*d*) E. J. Jung, B. H. Park and Y. R. Lee, *Green Chem.*, 2010, **12**, 2003; (*e*) S. Kumar, D. Hernandez, B. Hoa, Y. Lee, J. S. Yang and A. M. Curdy, *Org. Lett.*, 2008, **10**, 3761; (*f*) M. Rawat, V. Prutyanov and W. D. Wulff, *J. Am. Chem. Soc.*, 2006, **128**, 11044; (*g*) O. A. Fedorova, F. Maure, A. V. Chebunkova, Y. P. Strokach, T. M. Valova, L. G. Kuzmina, J. A. K. Howard, M. Wenzel, K. Gloe, V. Lokshin and A. Samat, *J. Phys. Org. Chem.*, 2007, **20**, 469; (*h*) S. Delbaer, J. C. Micheau and G. Vermeersch, *J. Org. Chem.*, 2003, **68**, 8968.
14 (*a*) P. B. Alper, C. Meyers, A. Lerchner, D. R. Siegel and E. M. Carreira, *Angew. Chem., Int. Ed.*, 1999, **38**, 3186; (*b*) A. Ashimori, B. Bachand, L. E. Overmann and D. J. Poon, *J. Am. Chem. Soc.*, 1998, **120**, 6477; (*c*) T. Matsuura, L. E. Overmann and D. J. Poon, *J. Am. Chem. Soc.*, 1998, **120**, 6500.
15 Y. Han and M. Xia, *Curr. Org. Chem.*, 2010, **14**, 379.
16 R. Menegatti, *Green Chemistry – Environmentally Benign Approaches*, ed. M. Kidwai and N. K. Mishra, InTech, 2012, ch. 2, pp. 13–32. Available from: http://www.intechopen.com/books/green-chemistry-environmentally-benign-approaches/green-chemistry-aspects-for-knoevenagel-reaction.
17 (*a*) P. Verdía, F. Santamarta and E. Tojo, *Molecules*, 2011, **16**, 4379; (*b*) C. Wang, Z. Guan and Y. He, *Green Chem.*, 2011, **13**, 2048.
18 U. R. Pratap, D. V. Jawale, R. A. Waghmare, D. L. Lingampalle and R. A. Mane, *New J. Chem.*, 2011, **35**, 49.
19 *Handbook of Pharmaceutical Excipients*, ed. R. C. Rowe, P. J. Sheskey and P. J. Weller, Pharmaceutical Press, London, 4th edn, 2003.
20 M. Seifi and H. Sheibani, *Catal. Lett.*, 2008, **126**, 275.
21 J. C. Xu, W. M. Li, H. Zheng, Y. F. Lai and P. F. Zhang, *Tetrahedron*, 2011, **67**, 9582.
22 J. M. Khurana, B. Nand and S. Kumar, *Synth. Commun.*, 2011, **41**, 405.
23 R. J. Kalbasi and N. Mosaddegh, *Catal. Commun.*, 2011, **12**, 1231.
24 K. Singh, J. Singh and H. Singh, *Tetrahedron*, 1996, **52**, 14273.
25 H. Zhi, C. Lu, Q. Zhang and J. Luo, *Chem. Commun.*, 2009, 2878.
26 A. Patra and T. Mahapatra, *J. Chem. Res.*, 2010, **34**, 689.
27 S. Abdolmohammadia and S. Balalaieb, *Tetrahedron Lett.*, 2007, **48**, 3299.
28 Y. Li, H. Chem, C. Shi and S. Ji, *J. Comb. Chem.*, 2010, **12**, 231.
29 Y. Zou, Y. Hu, H. Liu and D. Shi, *ACS Comb. Sci.*, 2012, **14**, 38.
30 N. Bicak, *J. Mol. Liq.*, 2005, **116**, 15.