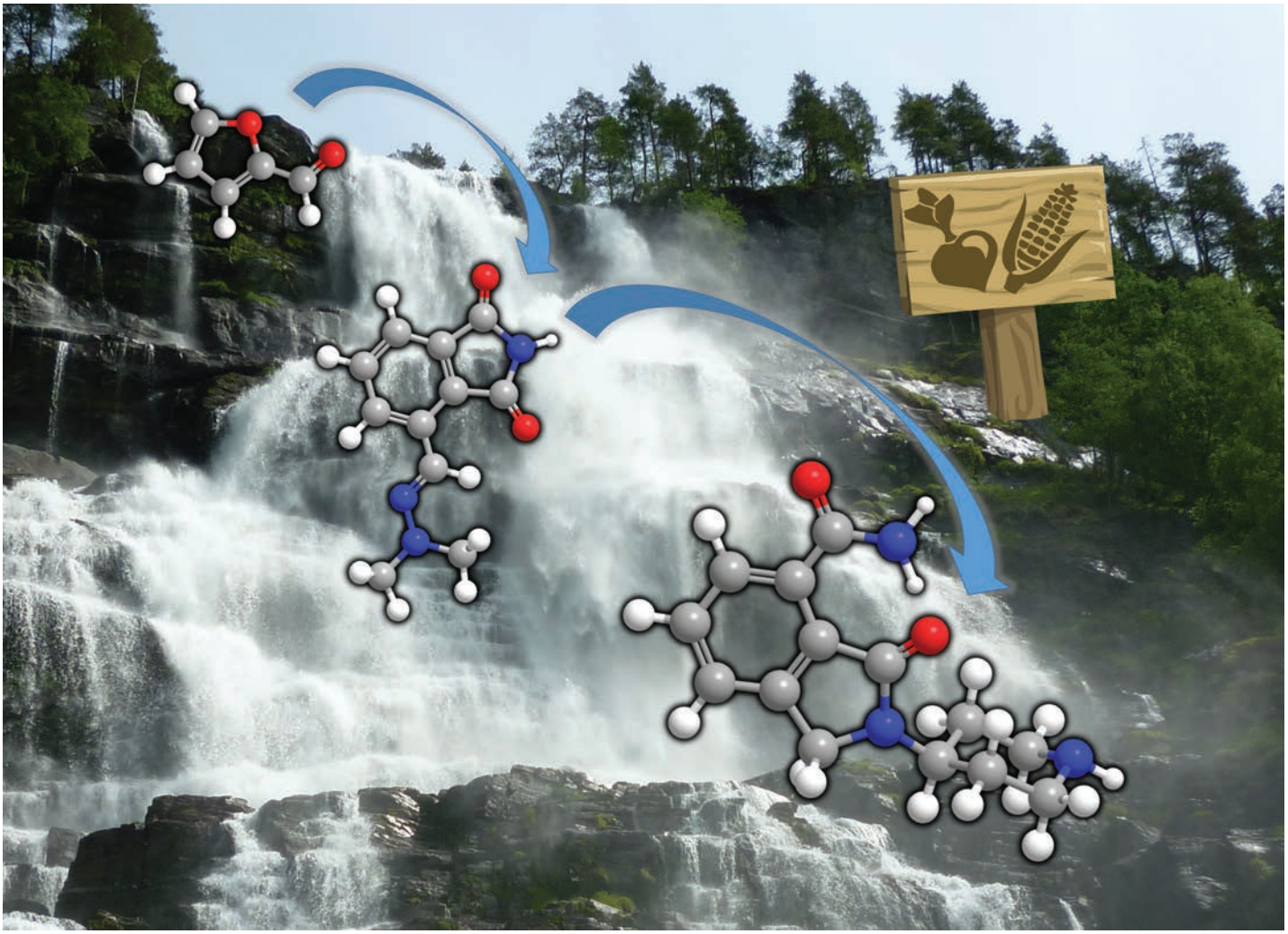

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Chemical cascades in water for the synthesis of functionalized aromatics from furfurals†

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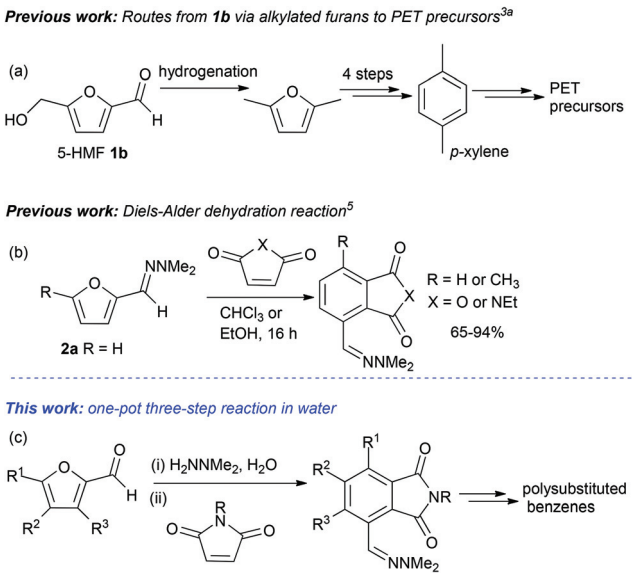
One-pot synthetic routes from furfurals to polysubstituted aromatic compounds have been developed in water, without the need for any organic solvents. The reaction proceeds *via* an uncatalysed, one-pot reaction cascade through formation of a hydrazone derivative, *in situ* cycloaddition with a dienophile, then aromatisation. A range of substituted phthalimides can be accessed with complete control over the substitution pattern. The reaction was also extended to other dienophiles and the diene 2-furylacrolein. The phthalimide products were further elaborated to produce a variety of polysubstituted benzenes including pharmaceutically relevant compounds.

Introduction

Furfural **1a** and 5-(hydroxymethylfurfural) (5-HMF) **1b** are renewable chemical feedstocks obtained from the hydrolysis and dehydration of cellulosic biomass, which is available from plant waste matter.[1] The use of furans in Diels–Alder cycloaddition reactions has been well documented: in general good yields have been observed in reactions between electron rich furans such as 2,5-dialkylated furans or 3-alkoxyfurans and electron deficient dieneophiles.[2] However, for many substrates Lewis acid catalysts, high temperatures/pressures or a large excess of the furan are required.[3] Of particular recent interest is the use of biomass-derived furans such as 2,5-dimethylfuran for the preparation of *p*-xylene for applications in polyethylene terephthalate (PET) synthesis, and one of the first synthetic routes required a lengthy reaction sequence using multiple reagents/catalysts (Scheme 1a).[3a] A more recent strategy employed the direct reaction of 2,5-dimethylfuran and ethylene in the presence of Lewis acid or heterogeneous acid catalysts at high temperature and pressure to generate *p*-xylene.[3b]



Scheme 1 Use of furfurals in routes to aromatic compounds.

Since 2,5-dimethylfuran is generated by the reduction of 5-HMF **1b**, a new strategy has been reported involving first the oxidation of **1b**, then reaction with ethylene at high temperature to generate 4-(hydroxymethyl)benzoic acid for subsequent conversion into PET precursors.[4] An alternative approach to the use of catalysts or forcing reaction conditions in furan Diels–Alder cycloadditions, is modification of the electron-withdrawing aldehyde moiety in biomass derived furans. For example, furfural dimethylhydrazone **2a**, prepared from furfural **1a**, was reacted with maleic anhydride or *N*-ethyl maleimide **3a** in chloroform to give aromatic products *via* a Diels–Alder-dehydration cascade in 65%–94% yield (Scheme 1b).[5] The approach utilising **2a** and maleic anhydride was subsequently used to generate phthalimides for the treatment of cutaneous lupus, and thalidomide analogues developed for the treatment of hematological cancers.[6,7]

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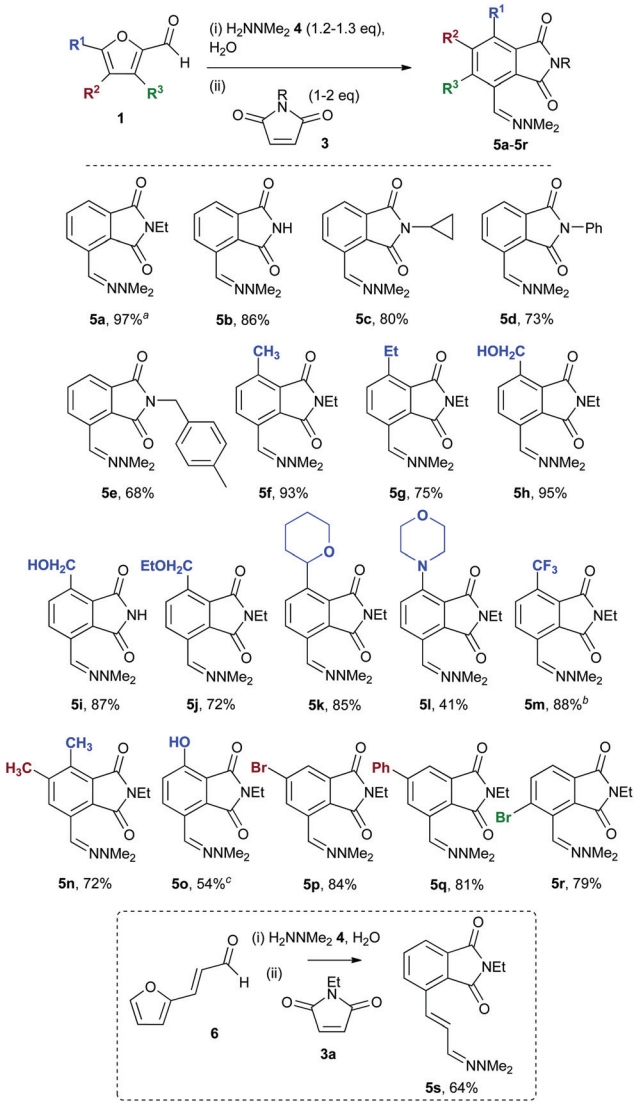
†Electronic supplementary information (ESI) available: Experimental procedures, ^{1}H NMR and ^{13}C NMR spectra, and compound characterisation data. See DOI: 10.1039/c5gc02935j

We are interested in developing non-petrochemical routes to functionalized pharmaceutically relevant aromatics using renewable chemical feedstocks and environmentally benign solvents such as water,[8] together with reaction cascades. It was envisaged that hydrazones such as **2a** had significant potential for developing an efficient route to polysubstituted benzenes from sustainable furfural building blocks, if efficient reaction conditions could be developed which avoided the need to employ toxic organic solvents or catalysts. Furthermore, it should be noted that polysubstituted benzenes (>3 substituents) are still often extremely difficult to prepare regioselectively, despite the fact that they have numerous applications in medicinal chemistry. Herein the synthesis of polysubstituted phthalimides is described from furfurals *via* a one-pot reaction cascade, which does not require organic solvents for either the reaction or for product purification. We also demonstrate subsequent modifications of the phthalimide products to access a selection of polysubstituted aromatic compounds (Scheme 1c).

Results and discussion

Initial studies using furfural **1a**, dimethylhydrazine **4** and *N*-ethylmaleimide **3a** focused on establishing the synthesis of the hydrazone **2a** and then the Diels–Alder-aromatisation two-step reaction in the same solvent – one with a good environmental profile for subsequent combination into a reaction cascade.[9]

While hydrazones are traditionally prepared by heating at reflux in organic solvents under dehydrating conditions, they have also been prepared in refluxing aqueous–alcoholic solutions.[10] Interestingly, the formation of hydrazone **2a** was achieved in 76% yield at 50 °C in water, despite the fact that the reaction involves a dehydration; although the product required isolation *via* an organic extraction. Pleasingly, however, reaction of **2a** with maleimide **3a** in water[11] (also at 50 °C, pH 6) gave phthalimide **5a** in 94% yield, giving a combined 2-step yield of 71%. When performed as a one-pot sequential reaction under the same conditions (Scheme 2), **5a** was formed in 95% yield and could be isolated directly as it precipitated out of the aqueous reaction mixture. Scaling the reaction up to 20 g (of **1a**) gave **5a** in 97% isolated yield. This suggests that the cycloaddition reaction can drive the initial hydrazone formation to completion by consuming **2a**, as the two-step yield was considerably higher than that observed for the hydrazone formation alone in water. The simultaneous addition of all three reaction components (**1a**, **3a**, and **4**) gave **5a** in approximately 10% lower yield due to side reactions; for this reason the reaction with other substrates was performed as a one-pot reaction by initially mixing **1** + **4**, before adding **3** after allowing time for hydrazone formation to reach equilibrium. The general utility of the reaction sequence was exemplified using five maleimides (**3a–3e**) and 13 furfural derivatives (**1a**, **1b**, **1f–1r**) to give phthalimides **5a–5r**. In most cases, the total reaction time was less than 5 h for the conversion of **1** to **5** (Scheme 2). In addition, products were isolated



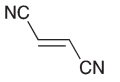
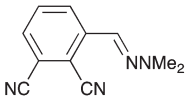
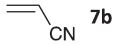
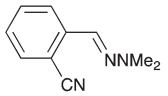
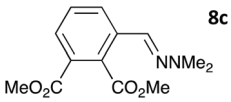
Scheme 2 Phthalimides **5a–5s** formed in the reaction cascade in water (pH 6), at 50 °C unless indicated otherwise; [a] 20 g scale; [b] the reaction was heated at 80 °C after addition of the maleimide; [c] 4-bromo-furfural was used.

by filtration with no organic solvents being used, making the reactions very amenable for scale-up. A range of different maleimides could readily be utilized, including **3b** (R = H) giving **5b** and **5i** in high yields (>85%). Phthalimides **5f–5m** were obtained in good to excellent yields from furfurals **1** with alkyl or heterocyclic groups at R^1, and from a dialkylated furfural (**5n**).

When R^1 = Br (**1o**), the phenolic product **5o** was generated due to the elimination of bromide during the aromatization step. With substituents at C-3 in the furfural (R^3 = Br) or C-4 (R^2 = Br, Ph), the corresponding phthalimides **5p–5r** were also formed in good yield. No reaction was observed with an aryl substituent at R^1.

The one-pot three-step cascade was also extended to furfuryl acrolein **6** to give **5s** in 64% isolated yield. In addition,

Table 1 Use of other dienophiles in the Diels–Alder dehydration cascade

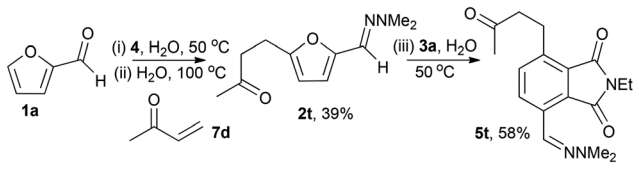
Dienophile	Reaction conditions	Product	Yield
 **7a**	100 °C 48 h	 **8a**	68%[a]
 **7b**	100 °C 24 h	 **8b**	24%[a]
 **7c**	100 °C 24 h	 **8c**	19%[b]

[a] Yield from the hydrazone **2a** (**2a** : dienophile, 1 : 2). [b] Yield from furfural **1a**.

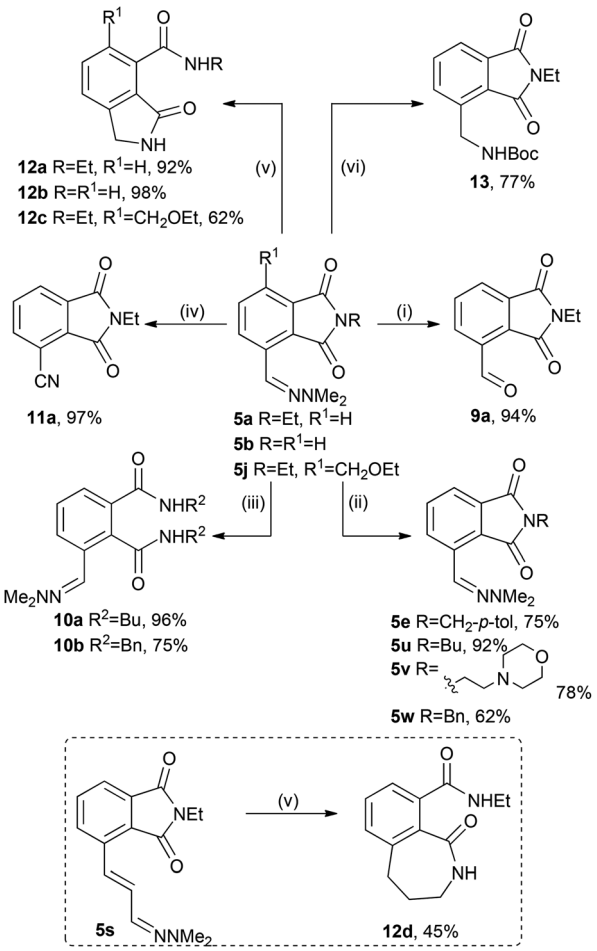
a selection of non-maleimide dienophiles were examined (Table 1). Fumaronitrile **7a** has previously been reacted with hydrazone **2a** in refluxing benzene with $SnCl_4$ catalyst, and **8a** was formed in only 13% yield due to extensive polymerisation.[5,12] With no catalyst, hydrazone **2a** reacted with **7a** in water to give **8a** in 68% isolated yield (Table 1). Acrylonitrile **7b** and dimethyl maleate **7c** were also used in reactions with the hydrazone **2a** or furfural **1a**, and **8b**/**8c** respectively were formed but in lower yield.

When the dimethylhydrazone **2a** was reacted with methyl vinyl ketone **7d** in water, a Michael-addition took place instead of a cycloaddition to give hydrazone **2t**. Optimisation of the first 2 steps gave **2t** in 39% yield (from **1a**), and subsequent cycloaddition and aromatisation gave **5t** in 58% yield that was readily isolated by filtration (Scheme 3). Hydrazone **2a** has previously been reported to undergo Michael addition to 1,4-naphthoquinone in boiling benzene,[5,12] however, it is notable here that conjugate addition to a less activated Michael-acceptor could be achieved in water without a catalyst.

Modification of phthalimide–hydrazones **5a**, **5b**, **5j** was investigated to demonstrate the versatility of the hydazones for the synthesis of polysubstituted benzenes. Hydrazone **5a** could be hydrolysed in excellent yield to the aldehyde **9a** (Scheme 4); **5b** readily underwent transamidation to a range of other phthalimides (**5e**, **5u**–**5w**) in 62%–92% yield using catalytic boric acid.[13] Notably, this reaction could be performed using **5b** isolated by filtration (but not dried) from the one-pot

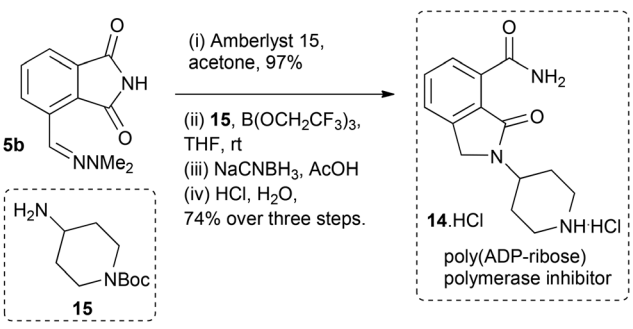


Scheme 3 One-pot formation of hydrazone **2t** in water and subsequent Diels–Alder cycloaddition and aromatisation in water.



Scheme 4 (i) Amberlyst 15, acetone; (ii) from **5b**, $B(OH)_3$, toluene/dioxane/2 eq. H_2O, RNH_2, 100 °C; (iii) excess RNH_2; (iv) magnesium monoperoxyphthalate (MMPP), MeOH, 0 °C; (v) H_2O/MeOH/HCO_2H, Pd/C, H_2; (vi) H_2O/MeOH/HCO_2H, Pd/C, H_2, then $(Boc)_2O$.

cascade. The phthalimide **5a** could also be ring opened with excess amine to give the diamides **10a**–**10b** in excellent yields. Oxidation of **5a** to the nitrile **11** was readily achieved in 97% yield, as was hydrogenation of **5a**, **5b**, **5j** to the amine, which



Scheme 5 Synthesis of poly(ADP-ribose) polymerase inhibitor **14**·HCl from furfural-derived phthalimide **5b**.

was either converted to lactams **12a–c** in 62–98% yield or directly isolated as the Boc-amine **13** in 77% yield. In a similar fashion hydrazone **5s** was reduced to tetrahydrobenzoazepin-1one **12d** in 45% isolated yield (Scheme 4).

Finally, synthesis of the poly(ADP-ribose) polymerase inhibitor and potential cancer chemotherapeutic **14**[14] was carried out using hydrazone **5b** (Scheme 5). Hydrolysis to the aldehyde **9b** was followed by imine formation with **15**/B$(OCH_2CF_3)_3$,[15] reduction then acid mediated Boc-deprotection and lactam formation to give the target compound **14** as the hydrochloride salt in 72% yield over the four step sequence.

Conclusions

In conclusion, one-pot cascade reaction sequences in water which provide access to polysubstituted phthalimides have been developed, without the need for organic solvents for either the reaction or product purification. The products generated are useful precursors to a range of polysubstituted benzenes including medicinally relevant compounds.

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