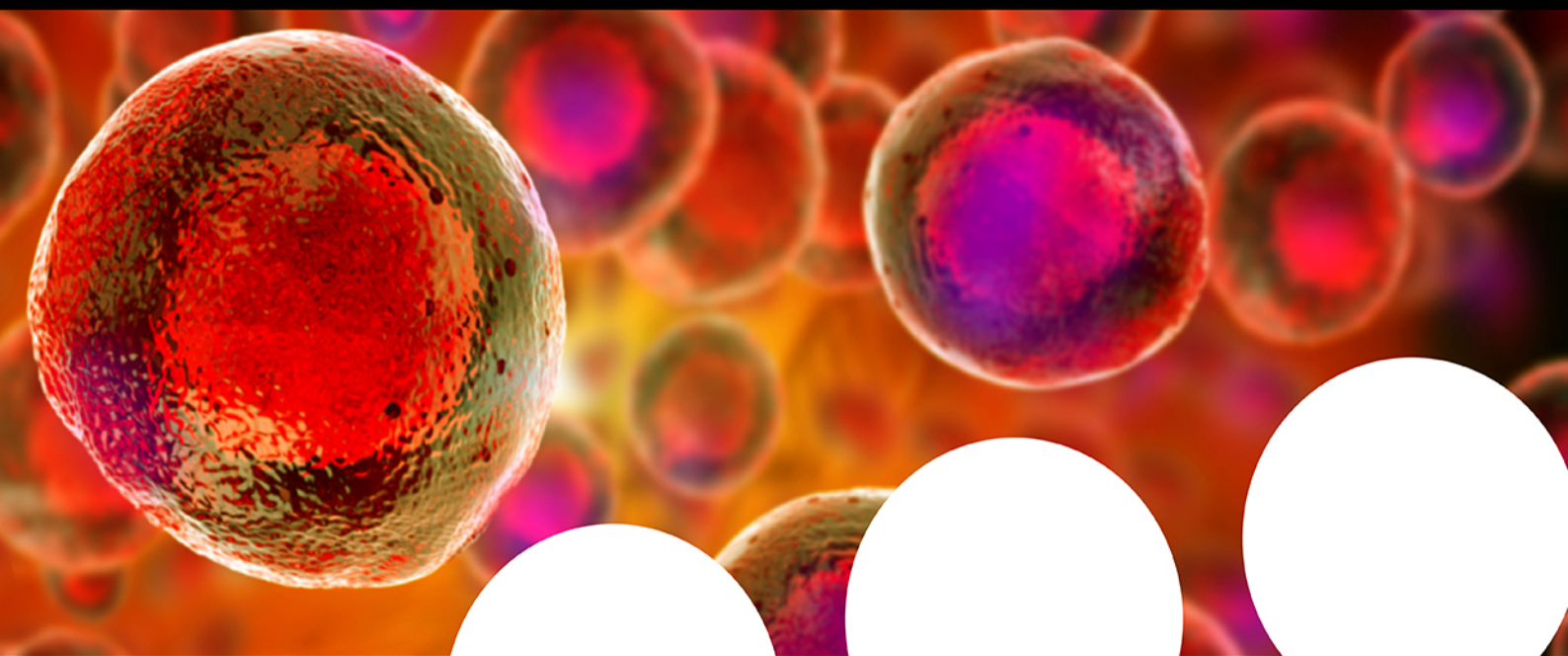


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Targeting Valuable Chemical Commodities: Hydrazine-mediated Diels-Alder Aromatization of Biobased Furfurals

Răzvan C. Cioc,^[a] Marc Crockatt,^[b] Jan C. van der Waal,^[b] and Pieter C. A. Bruijninx^{*,[a]}

A hydrazine-mediated approach towards renewable aromatics production via Diels-Alder aromatization of readily available, biobased furfurals was explored as alternative to the more classical approaches that rely on reactive but uneconomical reduced dienes (e.g., 2,5-dimethylfuran). To enable cycloaddition chemistry with these otherwise unreactive formyl furans, substrate activation by *N,N*-dimethyl hydrazone formation was investigated. The choice of the reaction partner was key to the success of the transformation, and in this respect acrylic acid

showed the most promising results in the synthesis of aromatics. This strategy allowed for selectivities up to 60% for a complex transformation consisting of Diels-Alder cycloaddition, oxabridge opening, decarboxylation, and dehydration. Exploration of the furfural scope yielded generic structure-reactivity-stability relationships. The proposed methodology enabled the redox-efficient, operationally simple, and mild synthesis of renewable (*p*-disubstituted) aromatics of commercial importance under remarkably mild conditions.

Introduction

The production of aromatic chemicals is of capital importance to many industries, as they are used in packaging, fabrics, coatings, plastics additives, solvents, pharmaceuticals, and so on. While the BTX hydrocarbons (benzene, toluene, xylenes) are the primary aromatic products of oil refining, most of their applications require considerable downstream processing, typically by oxidation, into functional (and more valuable) molecules such as terephthalic acid (benzene 1,4-dicarboxylic acid, TA), phthalic anhydride (PA), isophthalic acid, or the mellitic acids, among many others. For example, terephthalic acid is the most important aromatic product (yearly manufacturing scale of >80 Mt)^[1] and the third largest chemical commodity (by volume) in the world,^[2] its *meta* isomer and PA are also produced on a Mtpa scale.^[3]

Presently, the tremendous (and growing) demand for these aromatic products is as of yet exclusively met by fossil-based manufacturing processes. However, this linear approach is inherently incompatible with the environmental and societal realities of the 21st century. Sustainability requires one to

consider not only carbon neutrality, but also energy-efficiency and general environmental footprint of production. In addition to being nonrenewable-based, the extraction, separation, and derivatization of BTX is tedious and energy-intensive, particularly since key applications such as polyester synthesis demand highly pure monomers. Additionally, the oxidation of methylated benzenes to benzoic acids (via the Amoco process) is performed under highly corrosive conditions that require specialized reactors and is accompanied with solvent losses due to burning and the generation of hazardous off-gases and polymerization inhibitors as side-products.^[4]

Alternative (circular) manufacturing processes towards oxygenated aromatics are indeed highly needed. In this respect, non-edible lignocellulosic biomass represents an opportune starting point for the synthesis of high value renewable aromatics: indeed, this bio-feedstock is cheap, sufficiently available, and evenly distributed. Moreover, from a structural (i.e., atom- and redox-efficiency) point of view, there is a good chemical match between the bio-derived platform molecules, which typically bear high-oxidation state functional groups, and molecules such as TA and PA. Several approaches to convert bio-derived intermediates into oxygenated aromatics (TA in particular) have been explored in the last decade,^[5–10] among the various options, the furan Diels-Alder (DA) cycloaddition/dehydration approach stands out in terms of efficiency and versatility (Figure 1).^[11–13] Indeed, extensive research efforts directed at the conversion of the platform molecule 5-hydroxymethylfurfural (5-HMF)^[14–18] into TA via 2,5-dimethylfuran (DMF) and *p*-xylene allowed for near-perfect yields for the DA step (Route A).^[19] However, this route does not capitalize on the structural advantage of biomass over fossil feedstocks since it essentially strips all the oxygen off the bio-resource by redox chemistry during the forging of the aromatic ring. Indeed, the fully deoxygenated hydrocarbon *p*-xylene (0 wt% O) is a poor intermediate between the oxygenated feedstock 5-HMF (38 wt% O) and the product TA (39 wt% O). This so-called “redox-detour” non-productively consumes 3 equiv. of valuable

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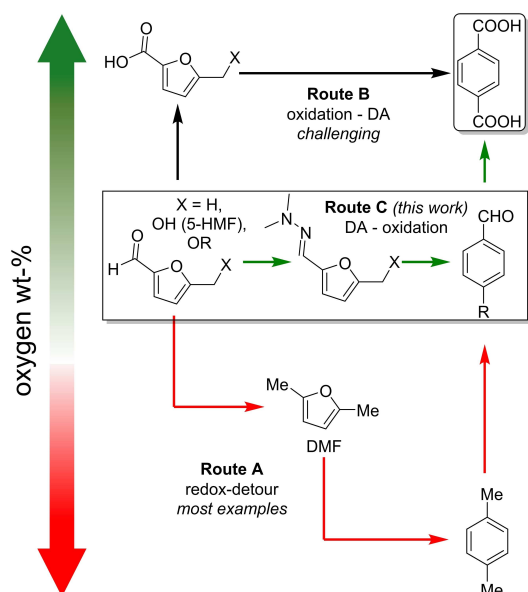


Figure 1. Synthesis of oxygenated aromatics via the furan Diels-Alder approach.

(and by necessity renewable) H_2 gas. Moreover, the need for re-oxidation requires the problematic Amoco oxidation to be still part of the route. These issues above hold even more for other furan-to-aromatics valorization efforts, as higher-value aromatics are typically more oxidized/functionalized, but routes are generally based on reduced furan feed. Acknowledging the disadvantages of this approach, more redox-efficient alternatives have emerged (Route B): a number of (mostly recent) reports disclose the use of oxidized derivatives of 5-HMF, [20–24] including FDCA (and its esters), [22,25–30] as dienes in the DA reaction. These efforts offer an improvement from the resource utilization point of view, but still often come with harsh reaction conditions, slow conversions, insufficient selectivities, poor catalyst recyclability, and so on. In between these redox extremes, there are many other possibilities of converting 5-HMF and related furfurals into oxygenated aromatics, including ultimately TA.

While formyl furans such as furfural and 5-HMF are the most readily accessible bio-based furans, they are notoriously poor dienes in cycloaddition chemistry. [11,13] Diels-Alder reactivity is enabled by chemical derivatization of the aldehyde group, with reduction reactions typically being pursued; redox-neutral activation approaches such as acetalization, [31–33] hydration, [34] or hydrazone formation [35–41] are relatively more difficult to implement in the context of renewable aromatics production, and examples thereof generally feature highly specific targets and narrow scope. For instance, while acetalization of the aldehyde does promote the cycloaddition, this functional group is incompatible with the generally acidic conditions required for dehydration (particularly since water is released in the process); alternatively, base-mediated E1cB aromatization is challenging due to the unfavorable geometric alignment of the bond orbitals involved. [42] Indeed, when it comes to the use of

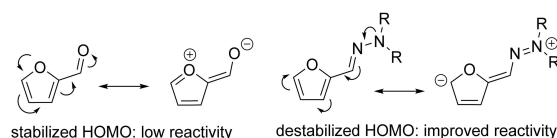
catalytic systems, it seems that the base-catalyzed aromatization is only successful with cyano-substituted oxanorbornene acetals (e.g., acrylonitrile as dienophile). [31,32] Further research efforts to extend the available toolbox of redox-neutral formyl furan activation are therefore still needed. Herein we report on our study of an alternative method for redox-neutral activation, in which bio-derived furfurals are activated as hydrazones prior to DA cycloaddition (Route C). In combination with the use of acrylic acid as dienophile, this option in principle enables a redox-efficient, operationally simple, and mild synthesis of renewable (*p*-disubstituted) aromatics of commercial importance.

Results and Discussion

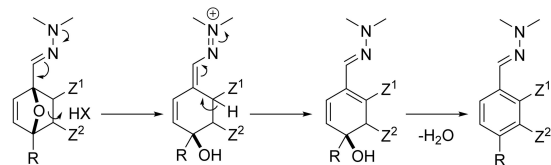
Reaction optimization

The general idea behind all these different furfural activation strategies is to reverse or alleviate the electron-withdrawing capabilities of the formyl substituent in order to raise the highest occupied molecular orbital (HOMO) energy level of the furan diene and thus improve the kinetics of the cycloaddition, according to the frontier molecular orbital (FMO) theory [43] (Scheme 1A). However, it is important to note that modulating the electronic properties of the furan 2- (and 5-) substituent(s) also strongly impacts the subsequent dehydration step. In this regard, formyl derivatization with a hydrazine auxiliary stands out as highly beneficial, as the hydrazone group formed at the

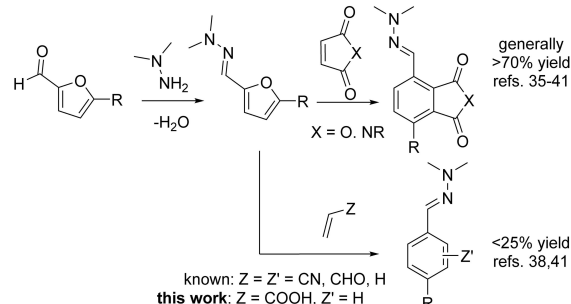
(A) furfural hydrazones: kinetic activation



(B) furfural hydrazones: (often) spontaneous, mild aromatization



(C) furfural hydrazones state-of-the-art: synthesis and DA scope



Scheme 1. Use of furfural hydrazones in DA cycloadditions.

adduct bridgehead position substantially reduces the barrier of ether bridge fission and dehydration; aromatization typically occurs spontaneously (even at temperatures as low as 25 °C, for example with maleic anhydride as dienophile, and generally below 100 °C, Scheme 1B); this in sharp contrast to most other furan DA adducts.^[11]

The simplicity of hydrazone synthesis and the relative ease with which the auxiliary can in principle be recycled greatly recommends the use of furfural hydrazones in the production of renewable aromatics. On the other hand, furfural hydrazones are rather unstable molecules, as other pathways than dehydration are also accessible upon activation. Thus, the selective synthesis of aromatics is presently limited to combinations primed for aromatization (i.e., with very reactive dienophiles, such as maleic anhydride and maleimides).^[35–41] These adduct combinations afford 1,2,3(4)-substituted products of considerably less commercial importance than the mono- and disubstituted benzenes currently used in bulk. Indeed, while highly desired, the use of monoactivated (acrolein, acrylonitrile)^[38] or nonactivated dienophiles (ethylene)^[41] produces only modest selectivities for the targeted aromatic products and still represents a major challenge in the field (Scheme 1C).

With these considerations and some recent reports on the synthesis of TA from DMF and acrylic acid in mind,^[44–47] we decided to investigate the combination of furfural hydrazones with this dienophile of intermediate reactivity. Our aim was to explore the impact of balancing the redox and carbon economy of the route, and in this respect, we evaluated several bio-based furfural hydrazones with an increasingly oxidized substituents at the furan 5-position, starting from Me (1a) as will be detailed below. Importantly, acrylic acid is a convenient bio-derived building block, accessible from biomass in 100% carbon yield either from glycerol or lactic acid.^[48] In terms of reactivity, our expectation was that the DA cycloaddition would still occur at a reasonably low temperature, despite the less activated nature of the furan diene relative to DMF. Spontaneous dehydration was anticipated to occur with concomitant decarboxylation,^[49] producing the targeted valuable mono- or *p*-disubstituted benzene products while avoiding potentially challenging regioselectivity control in the DA step.^[50] In this regard, acrylic acid functions as a more reactive ethylene surrogate, providing access to the same products, but under milder conditions; importantly, the overall carbon yield is the same (89%): both routes sacrifice one carbon atom; for the former, this is during the aromatization step and for the latter, during the fermentation of sugars to bioethanol and its subsequent dehydration to ethylene.

Our hypotheses concerning reactivity were confirmed by preliminary experiments with the *N,N*-dimethyl hydrazone of 5-methyl furfural (1a). The desired product 3a was formed (with varying efficiency) in a broad range of organic solvents, with the free aldehydes 1'a and 3'a being also present, though generally in low amounts (Table 1). On the other hand, the regioisomeric benzoic acids *ortho*-4a and *meta*-4a were not observed (see mechanistic discussion).

A solvent screening identified MeCN and CHCl₃ as best-performing solvents in terms of yield and mass balance.

Table 1. Performance of the title reaction between 1a and 2a in various solvents.^[a]

Entry	Solvent	Conv. 1a ^[b] [%]	Yield [%]			Mass balance ^[c] [%]
			1'a	3a	3'a	
1	AcOEt	45	8	18	2	83
2	THF	26	12	6	0	92
3	dioxane	28	4	7	0	83
4	DMF	24	5	7	0	88
5	toluene	73	5	25	5	62
6	C ₆ H ₁₂	72	4	27	4	63
7	MeCN	65	6	35	4	80
8	CDCl ₃	76	3	46	6	79
9	iPrOH	50	6	21	3	80
10	1-PrCN	68	7	22	4	65
11	CO(OEt) ₂	56	7	21	3	75
12	CH ₂ Cl ₂	93	5	21	12	45
13	1-BuOH	59	5	23	3	72
14	water ^[d]	>95	3	<5	0	13
15	2a ^[e]	80	11	0	11	42

[a] General procedure: 1a (0.5 mmol) and 2a (2 equiv.) in 1 mL of solvent (0.5 M) in a sealed vial for 20 h at 100 °C. [b] Quantitation was done by crude ¹H NMR spectroscopy using mesitylene as external standard. [c] Defined as 1a + 1'a + 3a + 3'a. [d] 1 M concentration. [e] With 10 equiv. of 2a.

Subsequent experimentation revealed that the reactions in chloroform were not very robust and likely dependent on the solvent batch; in addition, as the use of chlorinated organic solvents is not ideal from an environmental point of view, MeCN was selected for further optimization. We proceeded to extensive screening tests to identify the optimal conditions for the synthesis of 3a, examining the effects of various parameters, such as temperature, concentration, stoichiometry, additives, and so on, on the reaction (see Supporting Information for details). Despite our efforts, the results obtained in our initial attempt (Table 1, entry 7) ultimately proved the best. The selectivity of the reaction plateaued at around 50–70%, likely due to partial chemical incompatibility between the furfural hydrazone and the Brønsted acidic dienophile (see mechanistic discussion). Similarly, the study of the reaction profile (Figure 2) concluded that degradation reactions towards tarry polymeric structures prevail upon prolonged stirring and optimal performance is obtained at reaction times shorter than 20 h.

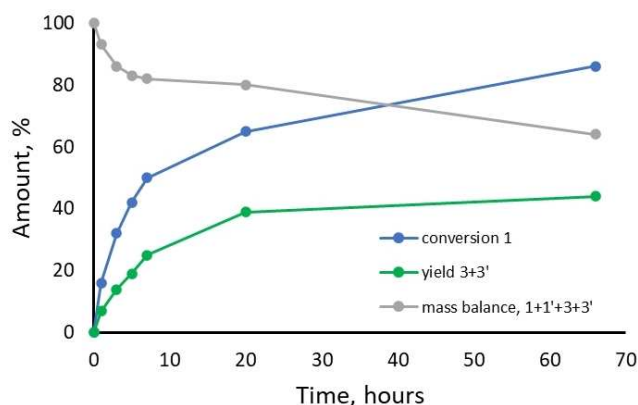


Figure 2. Synthesis of **3a** from furfural hydrazone **1a**: reaction profile in MeCN.

Reaction scope

With these improved reaction conditions in hand, we proceeded to evaluate the potential and, particularly, the limitations of this methodology in terms of scope, with regard to readily accessible bio-based furanic aldehydes (Table 2). Importantly, the preparation of furfural *N,N*-dimethyl hydrazones **1a–g** was easily achieved by mixing equimolar amounts of the corresponding furan aldehyde and *N,N*-dimethyl hydrazine in an organic solvent such as THF or AcOEt. The condensation is water-tolerant (see Supporting Information and refs. [37,38]) and therefore does not require a dehydrating agent.

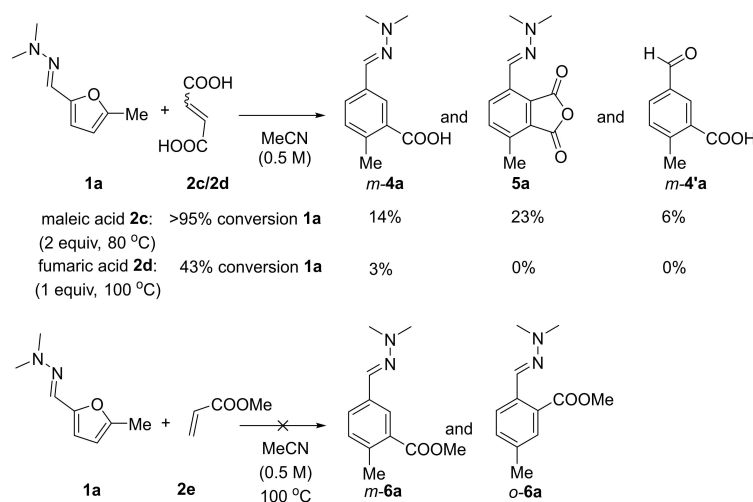
Variation of the diene structure showed that **1a** is most suited as diene in terms of productive conversion (60% selectivity at 65% conversion of **1a**), with a combined yield for **3a** + **3'a** of 39%. The more oxidized furans performed consid-

erably less well. Unsubstituted furfural hydrazone **1b**, for example, gave lower yields, presumably due to a more facile degradation under the reaction conditions (Table 2, entry 2). This result is in line with literature observations for the related conversion of methylated furans to aromatics: the presence of an additional methyl substituent at the furan 5-position greatly benefits the chemoselectivity of the overall transformation.^[20,24,51,52] 5-HMF-derived hydrazone and its ethyl ether analogue afforded disappointing yields, again due to competitive degradation side reactions (entries 3 and 4). Presumably, the presence of a leaving group in the structure of furans **1c** and **1d** contributes to the increased chemical lability of these hydrazones,^[53] according to the mechanism proposed in Scheme 2. This suggestion is supported by the ionization behavior of **1c** and **1d** seen in electron spray ionization mass spectrometry (ESI-MS) characterization, which shows expulsion of the leaving group (HO^- and EtO^- , respectively, see Supporting Information for details). The diformyl furan and carboxyl-substituted furfural hydrazones (**1e–g**) would be attractive precursors for the production of renewable terephthalic acid but showed little utility in this synthetic route. The presence of the additional electron-withdrawing substituent at the furan 5-position stabilizes the HOMO of the diene, diminishing its reactivity in [4 + 2] cycloadditions; this loss of reactivity is detrimental as degradation still occurs readily under the reaction conditions, particularly for **1f** (entry 6). An important decomposition pathway for this furan carboxylic acid is loss of CO_2 : 11% of furfural hydrazone **1b** and a total of 13% of the corresponding aromatic products **3b** + **3'b** were detected in the tarry reaction mixture. The methyl ester analogue **1f** is more stable with respect to degradation; however, this hydrazone delivered only a modest yield and selectivity towards **3f** (entry 7).

Table 2. Scope of aromatic products accessible from furfural hydrazones via the DA/dehydration route.^[a]

Entry	R ¹	Dienophile	3	Conv. 1 ^[b] [%]	1'	3	Yield [%] 3'	3 + 3'	Mass balance ^[c] [%]
1	Me	acrylic acid	3a	65	6	35	4	39	80
2	H	acrylic acid	3b	91	0	20	1	21	30
3	CH ₂ OH	acrylic acid	3c	97	1	6	2	8	12
4	CH ₂ OEt	acrylic acid	3d	90	1	12	2	14	25
5	CH=N–NMe ₂	acrylic acid	3e	47	1	5	0	5	59
6	COOH	acrylic acid	3f	94	0	12 ^[d]	1 ^[d]	13 ^[d]	19
7	COOMe	acrylic acid	3g	27	0	3	0	3	76
8	Me	methacrylic acid	3h	26	2	9	0	9	85
9 ^[e]	Me	methacrylic acid	3h	42	2	14	1	15	75
10 ^[e]	H	methacrylic acid	3i	78	0	23	0	23	45

[a] General procedure: furfural hydrazone **1** and dienophile (**2** equiv.) in MeCN (0.5 M) in a sealed vial for 20 h at 100 °C. [b] Quantitation was done by crude ¹H NMR spectroscopy using mesitylene as external standard. [c] Defined as **1** + **1'** + **3** + **3'**. [d] Together with extensive decomposition, decarboxylation of **1f** to **1b** occurred (11% of **1b** detected at the end of the reaction), with the production of **3b** as main aromatic product; the reported yield corresponds to **3b**. [e] Performed at 120 °C.



Scheme 2. Exploration of the dienophile scope of the reaction.

We then examined the dienophile scope of the reaction, looking at other renewable unsaturated carboxylic acids.^[8,54–56] The cycloaddition of **1a** with methacrylic acid^[57] was slow under the reaction conditions (entry 8). It is noteworthy that only the 2,4-dimethyl benzaldehyde hydrazone **3h** was identified as an aromatic product in the reaction. The exclusive formation of this regioisomer can be explained by FMO theory (i.e., by the enhanced orbital interaction between the diene and the dienophile in the transition state).^[43] Raising the reaction temperature to 120 °C (entry 9) led to only a modest increase in the yield, at the expense of selectivity. Similarly, cycloaddition of furfural hydrazone **1b** and methacrylic acid, targeting potentially selective production of *o*-tolualdehyde **3'i** en route to phthalic anhydride as another valuable aromatic target, showed the same issues (entry 10).

We then looked at the use of maleic acid and fumaric acid as dienophiles (Scheme 2). We expected that these bis-activated dienophiles would display higher reactivity than acrylic acid although it was anticipated that their increased relative acidity might promote degradation (see also Table 3). Maleic acid **2c** showed indeed enhanced reactivity, with a total of 43%

aromatics produced at nearly complete conversion of **1a** (at 80 °C). The main product was anhydride **5a**; it is not completely clear whether the ring closure occurs prior or subsequent to the cycloaddition/dehydration. Interestingly, the reaction is regioselective for the 2,5-disubstituted benzoic acid (*meta*-**4a**); this again confirms that decarboxylation is facile during the aromatization for the COOH substituent closest to the hydrazone activating group in the DA adduct (Scheme 3). This was equally observed for the reaction with fumaric acid **2d** as dienophile, where *meta*-**4a** was the sole detectable aromatic product, albeit in a very low yield; with this dienophile, the DA cycloaddition seems to be slow relative to competitive degradation. Finally, the COOH substituent as activating group for the dienophile proved critical for the reaction, as in combination with methyl acrylate **2e** no conversion was observed under the standard conditions. This difference in reactivity can be explained in line with the FMO theory: the lowest unoccupied molecular orbital (LUMO) of the acid was calculated to be considerably lower in energy than for the ester.^[58]

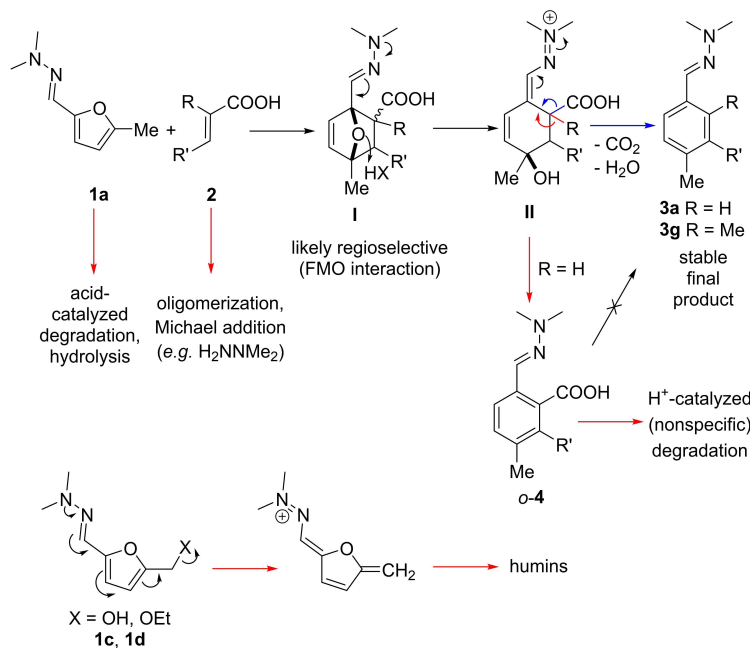
Mechanistic considerations

We performed several control experiments to gain more insight into the reaction mechanism and better understand the limitations of this chemistry. Methyl-furfural hydrazone **1a** was found to be rather sensitive to the action of (catalytic) Brønsted or Lewis acids (Table 3). For instance, in the presence of excess benzoic acid (entry 2), a carboxylic acid with comparable acidity to the acrylic acid dienophile, roughly a quarter of **1a** was lost in degradation reactions. Interestingly, the presence of water (up to 2 equiv; stoichiometric water is cogenerated in the DA/aromatization reaction) does not seem to lead to further degradation (entry 3). In the presence of a Lewis acid such as Zn(OTf)₂ (entry 5), extensive degradation takes place; this sensitivity precludes the use of the catalysts typically used to enable cycloaddition reaction at a lower temperature (see

Table 3. Hydrazone **1a** stability evaluation and control experiments.^[a]

Entry	Deviation from conditions	Recovery ^[b] [%]	Hydrolysis ^[b] [%]
1	stability 1a in the absence of 2a	99	0
2	with PhCOOH instead of 2a (2 equiv.)	76	0
3	entry 2, with water (2 equiv.)	76	2
4	with TFA (10 mol %) instead of 2a	92	0
5	with Zn(OTf) ₂ (10 mol %) instead of 2a	63	0
6	stability 1'a	95	n.a.
7	stability 2a in the absence of 1a	95	n.a.
8	stability o-4b	–	– ^[c]
9	stability o-4b in the absence of 2a	45	7

[a] General procedure: **1a** (0.5 mmol) and **2a** in MeCN in a sealed vial, 20 h at 100 °C. [b] Quantitation was done by crude ¹H NMR spectroscopy using mesitylene as external standard. n.a. = not applicable. [c] Could not be accurately determined, extensive decomposition.



Scheme 3. Reaction mechanism and alternative pathways.

Supporting Information). The activation of furfurals by conversion to the hydrazones seems to be responsible not only for the desired reactivity, but also for the degradation. In the presence of acrylic acid, **1'a** remains essentially unchanged (entry 6) and no DA reaction was observed, in line with the well documented reluctance of formyl furans to engage in [4+2] cycloadditions.^[31,34,59,60] The dienophile, acrylic acid **2a**, is also stable under the reaction conditions according to the control experiment in entry 7, but oligomerization initiated by the generation of nucleophilic species during the reaction (e.g., free hydrazine by hydrolysis of **1a**) is a potential risk. On the other hand, we were intrigued to find that the *N,N*-dimethyl hydrazone of *o*-formyl benzoic acid **o-4b** is highly prone to degrade under the mildly acidic conditions of the experiment (entry 8), with a fairly limited chemical stability even in the absence of **2a** (entry 9). This observation suggests that if formed at all, an *o*-COOH-substituted aromatic hydrazone (**o-4**) would actually be a non-productive intermediate in the reaction; decarboxylation to yield **3a** must therefore be occurring during the dehydration and not afterwards. Thus, the monocyclic intermediate **II** (Scheme 3) is another potentially important checkpoint for chemoselectivity control, as only the decarboxylation channel can lead to a stable aromatic structure.

These control experiments allowed us to draw a mechanistic picture of the reaction (Scheme 3). We believe that the DA cycloaddition between **1a** and **2a** occurs regioselectively to yield the *ortho* adduct, in line with FMO predictions. With the assistance of the bridgehead hydrazone substituent, the fission of the oxabridge occurs readily at 100 °C, in analogy with other systems bearing substituents with positive mesomeric effects reported in the literature.^[61–64] Finally, to complete the generation of the aromatic core, either a proton or CO₂ is expelled.

As argued before, only the latter case is a productive process, as the *ortho* disposition of –CH=N–NMe₂ and COOH functional groups on a benzene ring seems to lead to a thermally labile structure and nonspecific degradation.

Thus, with furfural hydrazones as dienes, the Diels-Alder/aromatization sequence takes place selectively only in combination with highly reactive dienophiles like maleic anhydride^[35,36,41] and especially maleimides^[35–40] (as the high hydrolytic stability of the latter prevents the generation of detrimental acidic impurities that can catalyze degradation). With these addend combinations, the fast Diels-Alder reaction outcompetes non-productive pathways. When less reactive dienophiles (acrylonitrile,^[38] ethylene^[41]) are used, forcing the reaction conditions (higher temperatures, Lewis acid catalysts) also promotes deleterious side reactions, lowering the selectivity for aromatics. In this regard, acrylic acid stands out as monoactivated dienophile: its relatively high reactivity allows for relatively mild conditions and accordingly improved selectivities, in combination with the most robust furfural hydrazone **1a**. On the other hand, the Brønsted acidity of acrylic acid is an intrinsic challenge for this route, in particular for labile hydrazones (**1b–f**). In the context of bulk aromatic chemicals production, the hydrazone activation approach thus converges on the **1a/2a** couple, which, despite not completely circumventing the “redox-detour”, still offers a resource benefit/improved atom economy in the production of a versatile synthetic intermediate, **3a**.

Hydrazine recycling

The viability of routes that use auxiliaries for (redox-neutral) activation depends on the ease of recovery and recycling, in this case of the hydrazine. Fortunately, in contrast to other aromatic hydrazones,^[41] **3a** could be readily hydrolyzed under very mild acidic conditions to yield **3'a** (98% conversion) (Scheme 4). The auxiliary could be easily separated as the hydrochloride salt by extractive workup with high recovery (95%). The regeneration of **1a** from 5-methyl furfural **1'a** occurred readily, in aqueous solution, after adjusting the pH with ammonia.

As noted above **3'a** is a versatile intermediate platform for the production of various aromatics, including, potentially, TA. Obviously, from a redox-economy and accessibility point of view, 5-HMF **1'c** (and its oxidized variants at C5, **1e**, **1f**, and **1g**) would be the ideal raw material for the synthesis of renewable TA via the furan DA/dehydration route. Unfortunately, 5-HMF and derivatives, including **1c**, are chemically labile molecules,^[65,66] and the reactions have modest selectivity towards the aromatic targets (Table 2, entries 3 and 4). 5-Methyl furfural **1'a** is typically produced from 5-HMF (or 5-chloromethylfurfural, 5-CMF^[67,68]) at the expense of 1 equiv. of H₂; therefore, the proposed route does not completely bypass the "redox-detour" but does offer a considerable improvement in redox- and atom-efficiency (O in particular) over, for example, DMF as diene. Alternatively, **1a** could also be sourced from deoxy-carbohydrates (e.g., rhamnose),^[69] which would provide a better redox-match between the renewable resource and the targeted

aromatic product **3'a** (although current production capabilities for deoxy-sugars are obviously not aligned with the tremendous demand for chemical commodities). While the selectivity of the hydrazone route is admittedly moderate, this drawback can be compensated by the higher atom economy (see Supporting Information), the operational simplicity, and the energy efficiency of the process. The reaction conditions we employ herein are significantly milder compared to the state-of-the-art in furan-to-aromatics conversion; in addition, external pressure or expensive, tailor-made catalysts are not necessary.^[5] Particularly when compared to alternative redox-economical routes starting from furoic acids/esters, our system offers advantages in terms of energetic efficiency, while the level of selectivity is comparable.^[20,22] Finally, *p*-tolualdehyde **3'a** is a more convenient (and effectively demonstrated) intermediate towards TA than *p*-xylene, since the oxidation of an already oxygenated functional group (formyl) proceeds more easily than the oxidation of a methyl group (Amoco process); moreover, if performed electrochemically, 1 equiv. of valuable H₂ can be coproduced in the process,^[70] paving the way for a fully hydrogen-neutral overall transformation of 5-HMF into renewable TA (Scheme 4F; *p*-toluic acid is also a known intermediate in the Amoco oxidation).

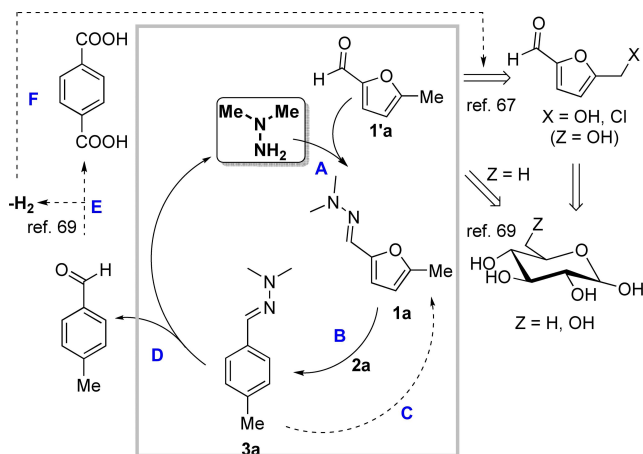
Conclusion

We demonstrate that Diels-Alder cycloaddition of furfural hydrazones can provide a more redox-efficient route for the conversion of readily accessible biomass-derived furfurals into various oxygenated aromatic molecules, including terephthalic acid precursors, provided that a balance is sought between reactivity and stability of addends. After derivatization as hydrazones, the otherwise unreactive formyl-furans engage in Diels-Alder cycloadditions with acrylic acid under mild conditions. Selectivity was found to critically depend on the nature of the furan 5-substituent (i.e., Me > H > CH₂OEt > CH₂OH > COOH), and substrate degradation pathways limiting the product yields have been proposed. The auxiliary *N,N*-dimethyl hydrazine can readily be recovered and reused. The improved atom utilization, operational simplicity, and energy efficiency recommend this approach as alternative to the classical "redox-detour" synthesis of terephthalic acid from 2,5-dimethylfuran.

Experimental Section

General synthesis of hydrazones

To a solution (THF or AcOEt) of the aldehyde, *N,N*-dimethyl hydrazine was added (1 equiv.). The mixture was stirred overnight at ambient temperature. Evaporation of the volatiles under vacuum typically led to sufficiently pure products. In larger-scale experiments (> 20 mmol), an aqueous phase visibly separated and was decanted prior to concentration of the organic phase. The crude furfural hydrazones have a characteristically brown color. The coloration can be somewhat reduced by passing the crude products over a silica gel column, but this step can be omitted.



- Water, rt (with NH₃ 2 equiv): 94% conversion of Me₂N-NH₂ upon recycle
- MeCN, **2a** (2 equiv), 100 °C, 20 h: 39% yield **3a**+**3'a** (66% based on **1a**+**1'a** recovery)
- Separation of **3a** and **1a** (distillation), recycle of **1a**
- Water/toluene, HCl (2 equiv), rt: >98% conversion **3a** 95% recovery Me₂N-NH₃Cl
- Oxidation of **3'a** to terephthalic acid (with coproduction of at least 1 equiv of H₂ if done electrochemically)
- Recycle of H₂ in the production of **1'a** from 5-HMF/5-CMF

Scheme 4. Recycling of the *N,N*-dimethyl hydrazine auxiliary and integration of the DA/dehydration route in the overall conversion of biomass to TA; steps A, B, and D are demonstrated in this study; steps E and F can be performed according to methodologies described in literature.

Some of the furfural hydrazones were found to slowly degrade upon storage in ambient conditions (especially **1b**, **1c**, and **1d**); for consistency, all hydrazones were stored in the freezer in nitrogen-flushed vials. Degradation did not take place under these conditions (for at least 3 months). Aryl hydrazones are typically pale-yellow oils or solids and stable upon storage.

General procedure for the DA cycloaddition/dehydration

In a microwave vial, the furfural hydrazone (1 equiv.) was weighed and diluted with the indicated solvent (generally 0.5 M concentration). Acrylic acid was then added (1–2 equiv.) and the vial was flushed with nitrogen prior sealing. The vial was heated on an oil bath at the indicated temperature for 1–24 h. The heating was then stopped, and the vial was allowed to reach ambient temperature before opening. Mesitylene was then added as external standard and the reaction mixture was diluted with CD₃CN prior to sampling and quantitative ¹H NMR spectroscopy.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: biomass conversion · cycloaddition · Diels-Alder · furfural · hydrazones

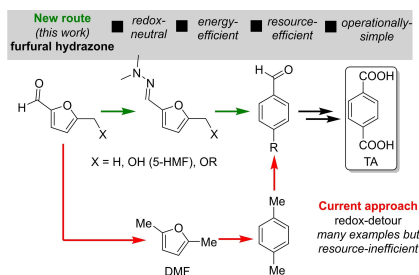
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RESEARCH ARTICLE

(Redox) detour? Not for furfural hydrazones! Derivatization as *N,N*-dimethyl hydrazone enables the use of furfurals in the production of renewable oxygenated aromatics via a redox-neutral Diels-Alder-based route. In combination with acrylic acid as dienophile, a tandem cycloaddition/decarboxylation/dehydration takes places in remarkably mild conditions en route towards valuable aromatic aldehydes.



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Targeting Valuable Chemical Commodities: Hydrazine-mediated Diels-Alder Aromatization of Biobased Furfurals

