Direct Diels-Alder reaction of chitin derived 3-acetamido-5-acetylfuran

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ABSTRACT: The Diels-Alder (DA) reaction of biomass derived furans is an emerging technology for the preparation of new molecular entities and "drop-in" commodity chemicals. In this work we address the challenge of the direct use of electron-poor furanic platforms as dienes through the use of an unexplored chitin derived furan, 3-acetamido-5-acetylfuran (3A5AF). The 3-acetamido group promoted a remarkable increase in the kinetics of the DA allowing for the preparation of 7-oxanorbornenes (7-ONB) at 50 ºC. Partial hydrolysis of the enamide to hemi-acylaminals was possible upon fine tuning of the reaction conditions, disabling retro-DA processes. Finally, DA reaction of the reduced form of 3A5AF allowed quantitative formation of 7-ONB in aqueous condition after 10 minutes. Certanly these are the first steps for expanding the toolbox of chitin derived 3A5AF as diene.

The Diels-Alder (DA) cycloaddition of furans have been subject of extensive research as of late, in particular, employing biomass derived furans such as furfural and 5-hydroxymethylfurfural (HMF).[1-3] Both these furans have been depicted as part of Bozel's list of top 10+4 biobased products from carbohydrates[4] and they have been reported in several seminal applications in a variety of areas (e.g. materials, energy, drug discovery).[3, 5-17] Importantly, furfural/HMF derivatives undergo reversible DA with dienophiles to yield 7-oxanorbornenes (7-ONB). This dynamic character has solely led to extensive research on understanding interactions and mechanistic nuances governing furan diene/dienophile DA and fine tuning reactants to bypass reactivity stability of the 7-ONB products issues (Scheme 1A).[18-23] In this sense, the furan DA technology has expanded to create stimuli responsive frameworks of the utmost importance in material chemistry[24], stable adducts usefull for drug discovery,[25] amongst others.[26] However, mostly electron rich furans are paired with electron poor dienophiles, meeting the conditions imposed by the Frontier Molecular Orbital (FMO) theory. This particularity renders the use of electron withdrawing biomass derived furfural and HMF *"as is"* a challenging task, as the electronic mismatch does not permit the reaction. Efforts to overcome this problem led to Brandvold in 2010 patenting the transformation of HMF to dimethylfuran (DiMF), towards the formation of biobased *p*-xylene[27] *via* DA in an elegant sequential strategy to prepare "drop-in" chemicals from bio-refinery derivatives. Further optimization[28-30] led to a one pot procedure from HMF to *p*-xylene.[31] A different approach designed by Ananikov and co-workers relied on the simple reduction of HMF to the corresponding 2,5-bis(hydroxymethyl)furan (BHMF), thus allowing the [4π+2π] cycloaddition

with maleimide. However, retro-DA of the 7-ONB hindered the isolation of the adduct, mandating for a tandem hydrogenation to bypass this issue.[18] Bruijnincx and coworkers recently reported a similar strategy, by trapping the DA adduct of furfuryl alcohol and activated acrylates yielding stable lactones.[19]
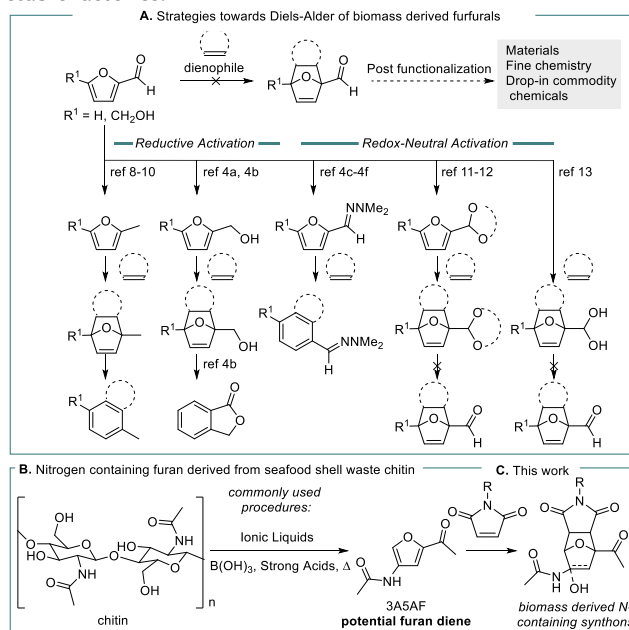
Scheme 1. A. Employed strategies towards Diels-Alder cycloadditions of biomass derived furfurals; B. Nitrogen containing furan 3A5AF derived from seafood shell waste chitin C. Direct Diels-Alder cycloadditions on 3A5AF (this work).

Unfortunately, these approaches require reduction of the biomass derived furfurals, which is not ideal when aiming at producing functionalizable derivatives. "Redox-neutral" strategies rely on masking the aldehydes either by hydrazone condensation[20-23, 32] (which often undergoes spontaneous post-DA aromatization) or the temporary installment of acetals, as reported by the groups of Jérôme and Dumesic.[32-36]

However, this latter example was shown that upon deprotection of the acetal, molecular orbital mismatch promotes complete retro-DA, affording HMF and maleimide. Noteworthy, Bruijnincx and coworkers observed that under concentrated aqueous solution, biomass derived furfurals underwent tandem DA reaction/aldehyde hydration in the presence of maleimides.[37] The same authors also observed a counterintuitive DA of carboxylic acids derived from furfural and HMF under basic conditions.[38]

All the advances on biomass furan DA chemistry have relied on lignocellulosic derived furans, leading to products that are themselves rich in carbon and oxygen.

However, an overlooked largely available waste byproduct, chitin, can be readily transformed into N-containing furan 3-acetamido-5-acetyl-furan (3A5AF).[39] Since over 5 million tons of seafood shells are produced, which contains 15-40% chitin by weight,[40] it can be envisioned that 3A5AF will play an important role as a key biomass derived *N*-containing synthon (Schem 1B).

Based on previous examples of furan DA reactions of substrates bearing 2-amino[41] and 3-amino substituents,[42] we enquired whether the amido group of 3A5AF allowed the direct DA reaction of this carbonyl-containing furan derivate with a model dienophile, thus bypassing orbital restriction of furfural, 2-acetyl furan (AF) or even HMF (Scheme 1C). The selected model was maleimide, being a bis-activated dienophile shown to undergo DA with a variety of furanic scaffolds. To strengthen the hypothesis, density functional theory (DFT) studies revealed a HOMO-LUMO gap for the 3A5AF/maleimide pair of 5.86 eV, in comparison with 6.35 eV for acetylfuran(AF)/maleimide and 6.32 eV for HMF/maleimide (Scheme 2A). The significant decrease of the HOMO by 0.5 eV of 3A5AF in comparison with AF was previously observed in indirect activation strategies of furfural/HMF to furfuryl alcohol/BHMF.[18, 35] Ananikov and coworkers recently observed a strong correlation between the HOMO of furan dienes and the free activation energy for the reaction.[43] Accordingly the mechanism of the reaction was evaluated by DFT performed at the M06L/6-311+G(d,p)/SMD(water)// M06L/6-31G(d) level of theory. Indeed a ΔG‡ difference > 3 kcal.mol⁻¹ was observed when comparing 3A5AF with AF and HMF. Moreover, a ΔG of -6.3 kcal.mol⁻¹ and -8 kcal.mol⁻¹ for endo-**1a** and exo-**1a** correspondingly (Scheme 2B) indicates the reaction is exergonic in nature, which should hinder retro cyclization processes.

Herein we explored the first direct DA reaction of biomass derived furans towards the preparation of novel N-containing synthons.
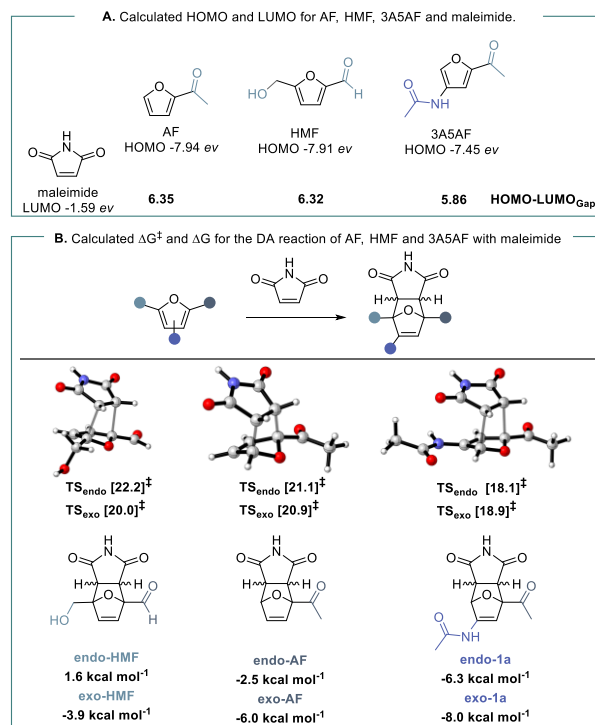
Scheme 2. A. Calculated HOMO and LUMO for AF, HMF, 3A5AF and maleimide. B. Calculated ΔG‡ and ΔG for the DA reaction of AF, HMF and 3A5AF with maleimide. DFT studies were performed at the M06L/6-311+G(d,p)/SMD(water)// M06L/6-31G(d) level of theory.
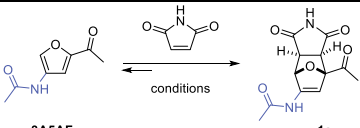
We initiated our endeavors by reacting 3A5AF with model unsubstituted maleimide in DMSO-d₆ under different temperatures (Table 1, Entries 1 - 5). We observed that the reaction afforded a single product in 80% yield under 50 ºC after 24 hours (Table 1, Entry 4), with no improvement of yield after 48h. This product was identified as the *exo* isomer of 7-ONB **1a** (for more information see SI).

Surprisingly, no *endo* product was detected by ¹H-NMR under the aforementioned reaction conditions. Limitations of the starting material solubility led to no conversion in most commonly used solvents for furan DA such as THF, dioxane, dichloromethane and chloroform (Table 1, Entries 6 - 9). Despite being soluble in acetonitrile and methanol, both led to poor yields of **1a** (Table 1, Entries 10 and 11).

The acceleration of DA reaction in water via hydrophobic effect has been thoroughly studied,[44] and has found its use on biomass furan DA chemistry.[37] In fact, one of the earliest reports on faster kinetics of DA reactions in water concerned furan and maleic anhydride.[45]

Aiming at improving the yields of DA adduct **1a**, the *on water* effect was studied by performing the reaction in DMSO-d₆:D₂O. Under these conditions, a new product **2a** was formed, corresponding to the partial hydrolysis of the enamide into a hemi-acylaminal (Scheme 3).

Table 1. Reaction optimization.[a]

Entry	Solvent	Temp. (ºC)	Time (h)	exo-**1a** (%)[b]
1	DMSO	rt	48h	0
2	DMSO	40	12	25
3	DMSO	50	12	43
4	DMSO	50	24	80
5	DMSO	50	24	80
6	THF	50	24	0
7	Dioxane	50	24	0
8	DCM	50	24	0
9	CHCl$_3$	50	24	0
10	MeCN	50	24	21
11	MeOH	50	24	35

[a] Reaction conditions: 3A5AF (6 mg, 0.035 mmol), maleimide (3.8 mg, 1.1 equiv), solvent (0.4 mL, 0.09M). [b] Yield determined by ^{1}H-NMR.

X-ray crystallography of a crystalline derivative from **2a** obtained from the reaction of 3A5AF and *N*-benzyl-maleimide revealed that the single diastereoisomer corresponds to the alcohol *cis* to the ether. Importantly, the new structure is incapable of undergoing retro-DA, which displaced the reaction equilibrium and allowed quantitative formation of **2a**. Moreover, the high solubility of **2a** allowed its purification through a simple washing with organic solvents followed by freeze drying. Competitive experiment using stoichiometric proportions of AF, and 3A5AF confirmed that only the latter underwent DA under these conditions, further highlighting the importance of the 3-amido group (See Figure S2).

When attempting the preparation of **2c** to obtain a crystal for Single-crystal X-ray crystallography, fine tuning of the reaction conditions was required. Interestingly, the reaction proceeded with the formation of the hemi-acylaminal **2c** under acidic conditions (buffer pH 2.6). Under basic conditions (buffer pH 8 and pH 10), the equilibrium is also shifted to **2c**, however hydrolysis of the maleimide hinders the utility of these conditions for the reaction. At pH 4 the reaction afforded the enamine product **1c**.

The scope for the enamine from **1** was extended to a variety of *N*-substituted maleimides (Scheme 4). Purification of the compounds was performed by simple extraction after trapping the excess maleimide with a thiol carboxylate, which widely contrasts with problematic purification steps reported for other 7-ONB from biomass derived furans.
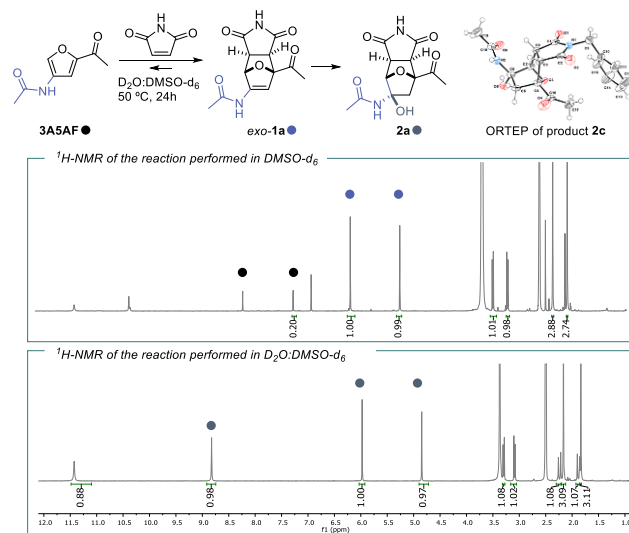
**Scheme 3.** Unexpected formation of hemi-acylaminal **2a** in water.

Moreover, products also tolerate chromatographic purification, with minimal formation of **2** in silica (See Figure S1). The reaction tolerates a variety of *N*-substituted maleimides, including alkyl (**1b**, **1c**), aryl (**1d**), polar *N*-subtituents such as C$_2$H$_4$OH (**1e**), C$_2$H$_4$OCH$_3$ (**1f**) and C$_2$H$_4$NHBoc (**1g**). The DA adducts **1** were obtained in excellent yield with negligible retro cyclization issues, with the exception of **1a** and **1g** where 20% and 14% of **3A5AF**, correspondingly, were observed upon column chromatography. Additionally, HPLC studies of the reversible character of the 7-ONB **1c** showed full reversibility after 5 min at 150 ºC (see SI for more information), which goes in line with the desirable properties for the use 7-ONB in heat-responsive materials.

A scope of hemi-acylaminals was also performed by carrying the reaction at buffered pH 2.6, yielding the desired products **2a-h** often in quantitative yields (Scheme 4). The products were easily purified through washing the aqueous media with organic solvent (ethyl acetate) followed by freeze drying.

To showcase the synthetic potential of the novel DA adduct, model reactions were performed with **1c** and **1d** (Scheme 5). Firstly, 7-ONB **1d** underwent acid promoted hydrolysis, yielding ketone **3** in high yield. Secondly, focusing on diversifying the electron rich olefin, epoxidation of **1c** with *m*CPBA followed by epoxide opening by 3-chloro-benzoic acid afforded **4** in 58% yield. Spectroscopic evaluation suggests the isomer depicted in Scheme 5, unfortunately a crystal to elucidate the conformation was unobtainable. Finally, hydrogenation of **1d** with palladium on carbon and H$_2$ furnished *N*-containing nor-cantharidin analogue **5** in 80% yield.
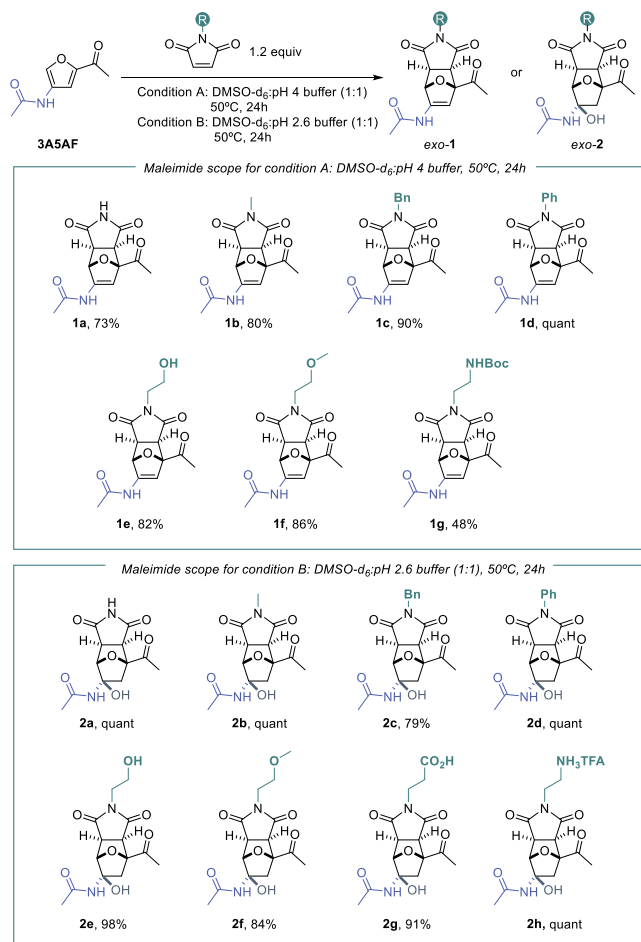
**Scheme 4.** Scope of the Diels-Alder reaction of 3A5AF.

Unfortunately, all attempts at aromatization of 7-ONBs **1a-d** and hemi-acylaminals **2a-d** either led to no conversion or decomposition (*i.e.* 80 ºC in HCl, 80ºC in HBr/AcOH, 0ºC to 80ºC in Ac₂O promoted by MsOH, 0ºC to reflux in DCE promoted by Cu(OTf)₂, ᵗBuOK in DMSO).
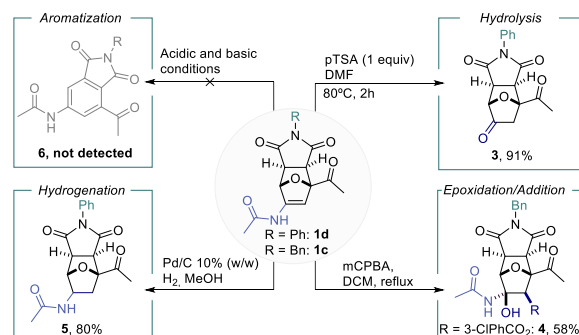
Scheme 5. Synthetic utility of DA adduct.

In line with the reported examples of BHMF and furfuryl alcohol, the corresponding alcohol **7** obtained from the reduction of 3A5AF was envisioned to react even faster that the parent ketone. To probe this reactivity, **7** was reacted with *N*-phenyl-

maleimide under aqueous conditions (Scheme 6). Indeed the alcohol was remarkably more reactive, achieving 99% yield at room temperature after 5 minutes. 7-ONB **8** was isolated as a mixture of diastereoisomers (*endo*-R, *endo*-S; *exo*-R, *exo*-S).
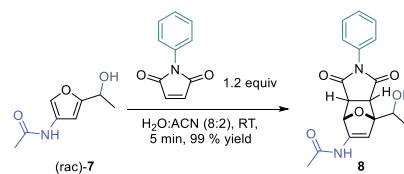
Scheme 6. DA reaction of alcohol **7** obtained from the reduction of 3A5AF.

In conclusion, the remarkable effect of the acetamide group in position 3 of the furan endorsed by *ab initio* studies, allowed for chitin derived 3A5AF to be used as the first biomass furan diene in DA reactions "*as is*". Fine tuning of the reaction conditions allows selective preparation of 7-oxanorbornenes (7-ONB) or tandem partial hydrolysis of the enamide to prepare 7-ONB hemi-acylaminal derivatives. Reaction of the corresponding alcohol allowed for a remarkably fast reaction affording the desired product in almost quantitative yield after 5 minutes at room temperature.

The beneficial effect of the 3-acetamide is observed by the mild reaction conditions in contrast with commonly employed harsh conditions which require high temperature or catalysts. Also the operational simplicity for the reaction setup/isolation is highly appealing for its application in areas such as materials, biomaterial chemistry and even biology

Nineteen new products were obtained from biomass derived 3A5AF in high yields.

This is the first step in expanding the toolbox of 3A5AF as diene, highlighting its potential growth into a key synthon for *N*-containing scaffolds, materials, and commodity aromatics.

ASSOCIATED CONTENT

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Author Contributions

The manuscript was written through contributions of all authors

Notes

Any additional relevant notes should be placed here.

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ABBREVIATIONS

DA, Diels-Alder; HMF, 5-hydroxymethylfurfural; 7-ONB, 7-oxanorbornenes; FMO, Frontier Molecular Orbital; DiMF, dimethylfuran; BHMF, 2,5-bis(hydroxymethyl)furan; 3A5AF, 3-acetamido-5-acetyl-furan; DFT, density functional theory; AF, acetylfuran.

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In this work 3A5AF, a biomass derived furan obtained from chitin, is used as diene in Diels-Alder reaction with maleimides. This is the first example of isolated 7-oxanorbornenes containing a ketone moiety obtained from biomass furanics. Moreover, the use of a chitin derivative allows incorporation of bio-based nitrogen in the final products, a challenge unmet by commonly used furanics such as furfural and 5-hydroxymethylfurfural.