Green Chemistry

PAPER

View Article Online
View Journal | View Issue



Cite this: *Green Chem.*, 2022, **24**, 7131

# A direct Diels–Alder reaction of chitin derived 3-acetamido-5-acetylfuran†

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Received 19th January 2022,
Accepted 24th May 2022

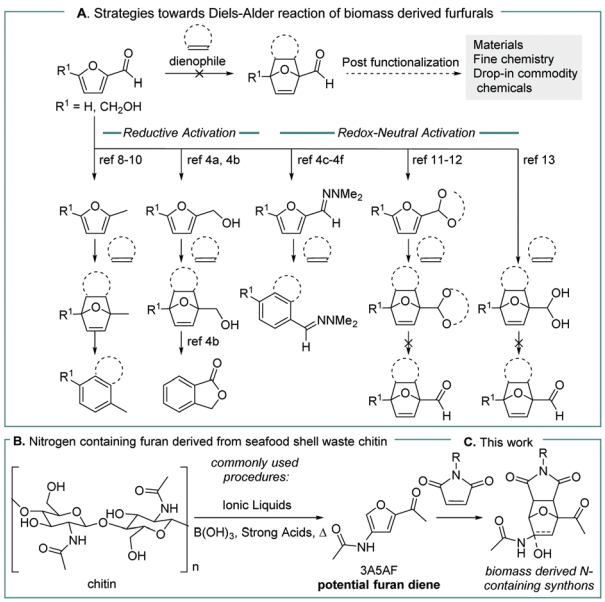
DOI: 10.1039/d2gc00253a

rsc.li/greenchem

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 reaction, allowing for the preparation of 7-oxanorbornenes (7-ONBs) at 50 °C. Partial hydrolysis of enamide to hemi-acylaminals was possible upon fine-tuning of the reaction conditions, disabling retro-DA processes. Finally, the DA reaction of the reduced form of **3A5AF** allowed quantitative formation of 7-ONBs under aqueous conditions after 10 minutes. Certainly, these are the first steps for expanding the toolbox of chitin derived **3A5AF** as a diene.



The Diels–Alder (DA) cycloaddition of furans has been the subject of extensive research of late; in particular, usage of 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 and drug discovery).[3,5–17] Importantly, furfural/HMF derivatives undergo reversible DA reactions with dienophiles to yield 7-oxanorbornenes (7-ONBs). This dynamic character has solely led to extensive research on understanding interactions and mechanistic nuances governing furan diene/dienophile DA reactions and fine-tuning of reactants to bypass the reactivity and stability of the 7-ONB products (Scheme 1A).[18–23] In this sense, the furan DA technology has expanded to create stimulus responsive frameworks of the utmost importance in materials chemistry[24] and stable adducts useful for drug discovery,[25] among 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 enables the use of electron withdrawing biomass derived furfural and HMF "as is", which is a challenging task, since the electronic mismatch does not permit the reaction. Efforts to overcome this problem led Brandvold in 2010 to patent the transformation of HMF into dimethylfuran (DMF), towards the formation of biobased *p*-xylene[27] *via* the DA reaction using an elegant sequential strategy to prepare "drop-in" chemicals from bio-refinery derivatives. Further optimization[28–30] led to the development of a one-pot procedure from HMF into *p*-xylene.[31] A different approach




**Scheme 1** (A) Employed strategies towards the Diels–Alder cycloadditions of biomass derived furfurals; (B) nitrogen containing furan **3A5AF** derived from seafood shell waste chitin; and (C) direct Diels–Alder cycloadditions on **3A5AF** (this work).

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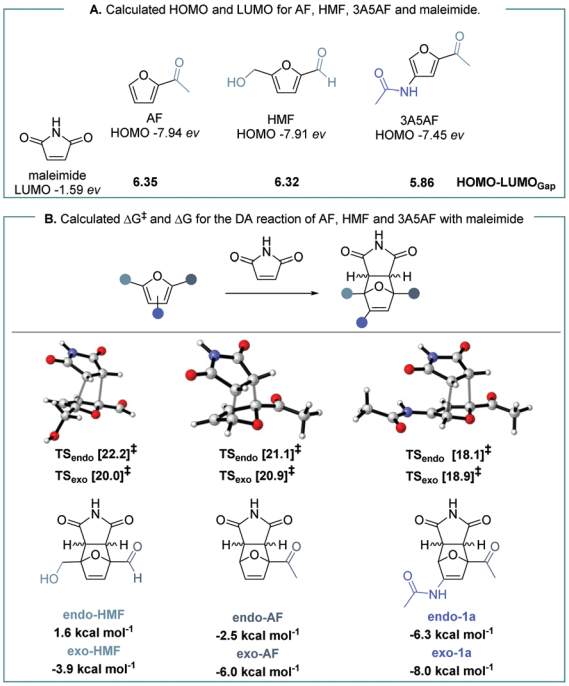
†Electronic supplementary information (ESI) available. CCDC 2141407. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d2gc00253a

designed by Ananikov and co-workers relied on the simple reduction of HMF into the corresponding 2,5-bis(hydroxymethyl)furan (BHMF), thus allowing the [4π + 2π] cycloaddition with maleimide. However, retro-DA reactions of the 7-ONB hindered the isolation of the adduct, mandating tandem hydrogenation to bypass this issue.[18] Bruijnincx and co-workers recently reported a similar strategy by trapping the DA adduct of furfuryl alcohol and activated acrylates, yielding stable lactones.[19] Unfortunately, these approaches require reduction of biomass derived furfurals, which is not ideal when aiming at producing functionalizable derivatives. "Redox-neutral" strategies rely on masking aldehydes either by hydrazone condensation[20–23,32] (which often undergoes spontaneous post-DA aromatization) or a temporary installment of acetals, as reported by the groups of Jérôme and Dumesic.[32–36] However, the latter example shows that upon deprotection of acetals, molecular orbital mismatch promotes the complete retro-DA reaction, affording HMF and maleimides. Notably, Bruijnincx and co-workers observed that in concentrated aqueous solution, biomass derived furfurals underwent the tandem DA reaction/aldehyde hydration in the presence of maleimides.[37] The same authors also observed a counterintuitive DA reaction of carboxylic acids derived from furfural and HMF under basic conditions.[38]

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

However, an overlooked largely available waste byproduct, chitin, can be transformed into N-containing furan 3-acetamido-5-acetyl-furan (**3A5AF**).[39] Since over 5 million tons of seafood shells are produced, which contain 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 (Scheme 1B).

Based on previous examples of furan DA reactions of substrates bearing 2-amino[41] and 3-amino substituents,[42] we investigated whether the amido group of **3A5AF** allowed the direct DA reaction of this carbonyl-containing furan derivative with a model dienophile, thus bypassing the orbital restriction of furfural, 2-acetyl furan (AF) or even HMF (Scheme 1C). The selected model was maleimide, a bis-activated dienophile shown to undergo DA reactions with a variety of furanic scaffolds. To strengthen the hypothesis, density functional theory (DFT) studies revealed a HOMO–LUMO gap of 5.86 eV for the **3A5AF**/maleimide pair, 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–LUMO gap by 0.5 eV for **3A5AF** in comparison with AF was previously observed in indirect activation strategies of furfural/HMF to furfuryl alcohol/BHMF.[18,35] Ananikov and co-workers recently observed a strong correlation between the HOMO–LUMO gap of furan dienes and the free activation energy for the reaction.[43] Accordingly, the mechanism of the reaction was evaluated by DFT calculations performed at the M06L/6-311+G(d,p)/SMD(water)//M06L/6-31G(d) level of theory. Indeed, a $\Delta G^{\ddagger}$ difference >3 kcal mol$^{-1}$ was observed when comparing **3A5AF** with AF and HMF. Moreover, a $\Delta G$ of −6.3 kcal mol$^{-1}$ and




**Scheme 2** (A) Calculated HOMO and LUMO for AF, HMF, **3A5AF** and maleimide. (B) Calculated $\Delta G^{\ddagger}$ and $\Delta G$ 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.

−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.

We initiated our endeavors by reacting **3A5AF** with a model unsubstituted maleimide in DMSO-d$_6$ at different temperatures (Table 1, entries 1–5). We observed that the reaction afforded a single product in 80% yield at 50 °C after 24 hours (Table 1, entry 4), with no improvement of yield after 48 h. This product was identified as the *exo* isomer of the 7-ONB **1a** (for more information, see the ESI†).

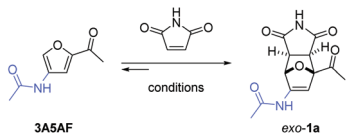
Surprisingly, no *endo* product was detected by $^1$H-NMR under the aforementioned reaction conditions. Limitations of the starting material solubility led to no conversion in most commonly used solvents for furan DA such as THF, dioxane, dichloromethane and chloroform (Table 1, entries 6–9). Despite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

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

Aiming at improving the yields of the DA adduct **1a**, the on-water effect was studied by performing the reaction in DMSO-d$_6$ : D$_2$O. Under these conditions, a new product **2a** was

**Table 1** Reaction optimization[a]



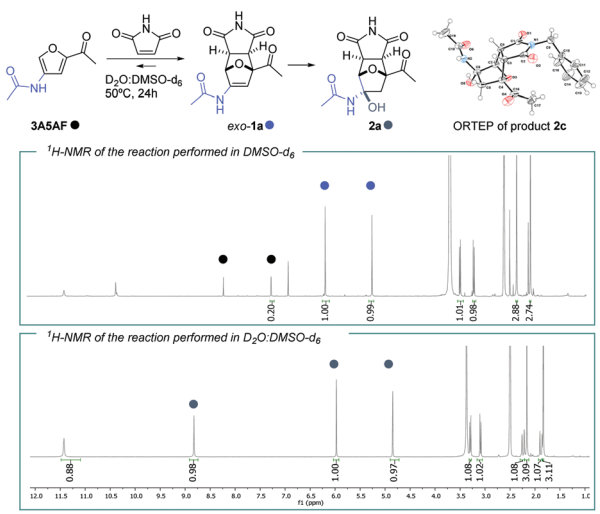

| Entry | Solvent | Temp. (°C) | Time (h) | *exo*-**1a**[b] (%) |
|---|---|---|---|---|
| 1 | DMSO | rt | 48 | 0 |
| 2 | DMSO | 40 | 12 | 25 |
| 3 | DMSO | 50 | 12 | 43 |
| 4 | DMSO | 50 | 24 | 80 |
| 5 | DMSO | 50 | 24 | 80 |
| 6 | THF | 50 | 24 | 0 |
| 7 | Dioxane | 50 | 24 | 0 |
| 8 | DCM | 50 | 24 | 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.), deuterated solvent (0.4 mL, 0.09 M). [b] Yield determined by direct $^1$H-NMR, through the integration of **3A5AF** and **1a**.

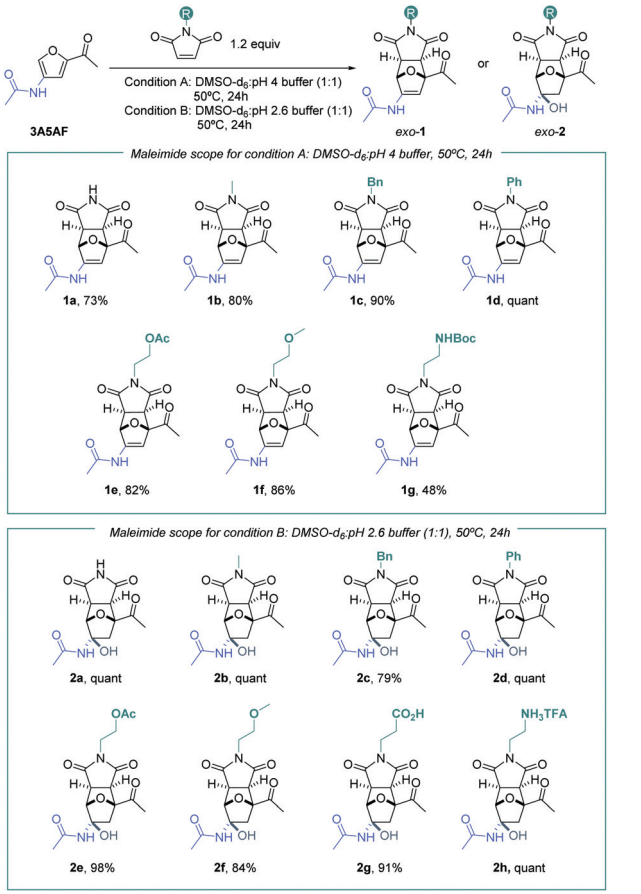
formed, corresponding to the partial hydrolysis of the enamide into a hemi-acylaminal (Scheme 3). X-ray crystallography of a crystalline derivative from **2a** obtained from the reaction of **3A5AF** and *N*-benzyl-maleimide revealed that the single diastereoisomer corresponds to the alcohol *cis* to the ether. Importantly, the new structure is incapable of undergoing retro-DA reactions, leading to displacement of the reaction equilibrium and allowing quantitative formation of **2a**. Moreover, the high solubility of **2a** allowed its purification through a simple washing with organic solvents followed by freeze drying. A competitive experiment using stoichiometric proportions of AF and **3A5AF** confirmed that only the latter underwent DA reactions under these conditions, further highlighting the importance of the 3-amido group (see Fig. 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 also shifted to **2c**; however, hydrolysis of the maleimide hindered 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-ONBs from biomass derived furans. Moreover, the products also tolerated chromatographic purification, with minimal formation of **2** in silica (see Fig. S1†). The reaction tolerates a variety of *N*-substituted maleimides, including alkyl (**1b** and **1c**), aryl (**1d**) and polar *N*-substituents such as $C_2H_4OAc$ (**1e**), $C_2H_4OCH_3$ (**1f**) and $C_2H_4NHBoc$ (**1g**). Unfortunately **3A5AF** was unreactive towards other dienophiles such as methyl acrylate and maleic anhydride. The DA adducts **1** were obtained in excellent yields with negligible retro-cyclization issues, with the exception of **1a** and **1g**, where 20% and




**Scheme 3** Unexpected formation of the hemi-acylaminal **2a** in water.




**Scheme 4** Scope of the Diels–Alder reaction of **3A5AF**.

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 °C (see the ESI† for more information), which goes in line with the desirable properties for the use of 7-ONBs in heat-responsive materials.

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

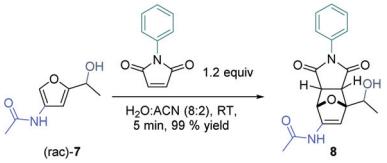
To determine the synthetic potential of the novel DA adduct, model reactions were performed with **1c** and **1d** (Scheme 5).

Firstly, the 7-ONB **1d** underwent acid promoted hydrolysis, yielding ketone **3** in a high yield. The ketone can be seen as a starting point for this diversity-oriented synthesis approach, being able to undergo various functional group transformations, *i.e.*, reduction, condensation with hydrazine and hydroxylamines and the Baeyer–Villiger oxidation. Additionally, the increased acidity of α-protons may aid in the discovery of aromatization conditions, as will be discussed further on.

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 revealed the isomer depicted in Scheme 5; unfortunately, a crystal to elucidate this conformation was not obtained. Finally, hydrogenation of **1d** with palladium on carbon and $H_2$ furnished an N-containing norcantharidin analogue **5** in 80% yield. The cantharidin scaffold has been thoroughly studied as an anticancer agent, usually targeting phosphor protein phosphatases (PP1 and PP2A).[46,47] This strategy may yield a diverse library of novel analogues upon further derivatization of the amide that can be used for biological screening.

Unfortunately, all attempts of aromatization of 7-ONBs **1a–d** and hemi-acylaminals **2a–d** either led to no conversion or decomposition (*i.e.* 80 °C in HCl, 80 °C in HBr/AcOH, 0 °C to 80 °C in $Ac_2O$ promoted by MsOH, 0 °C to reflux in DCE promoted by $Cu(OTf)_2$ and $^t$BuOK in DMSO).

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 than the parent ketone.[48] To probe this reactivity, **7** was reacted with *N*-phenylmaleimide under aqueous conditions (Scheme 6). Indeed, the alcohol was remarkably more reactive, affording 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**.

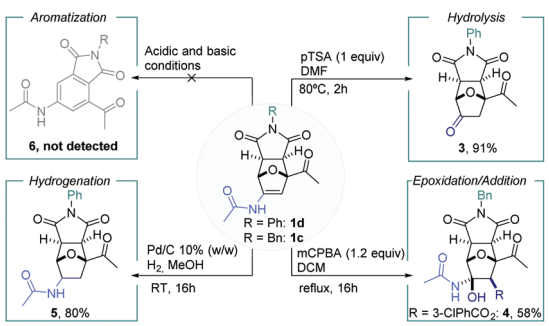
In conclusion, the remarkable effect of the acetamide group in position 3 of the furan, endorsed by *ab initio* studies, allowed for chitin derived **3A5AF** to be used as the first biomass furan diene in DA reactions "as is". Fine-tuning of the reaction conditions allows selective preparation of 7-oxanorbornenes (7-ONBs) 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 3-acetamide is observed under 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 and biomaterials chemistry and even biology.

Nineteen new products were obtained from biomass derived **3A5AF** in high yields. The introduction of renewable nitrogen is of the utmost importance, given the dependence of the Haber processes on the preparation of ammonia, the most common nitrogen source for fine and commodity chemicals.[49,50] This leads to the consumption of *circa* 1.5% of the total world energy consumption for the production of ammonia. Considering the potential of aromatization of 7-ONBs, this work paves the way for the preparation of bio-based anilines, which are commonly prepared from oil-derived benzene under harsh conditions (nitration followed by hydrogenation of nitrobenzene).[51] Future applications of this chemistry can lead to considerable advances in sustainability, not only by using renewable raw materials but also by reducing the consumption of hydrogen and the harsh conditions currently in use.[52]

Ongoing diversification studies will be followed by intense biological screening aiming at discovering novel scaffolds from chitin for drug discovery.

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




**Scheme 5** Synthetic utility of the DA adduct.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support from Fundação para a Ciência e a Tecnologia (SFRH/BD/120829/2016; PTDC/QUI-QOR/32008/2017; UIDB/04138/2020; UIDP/04138/2020, SFRH/BD/120119/2016, PD/BD/143162/2019) is gratefully acknowledged. The project leading to this research has received funding from the European Union's Horizon 2020 research and innovation programme under the grant agreement no. 951996. Fausto Queda is thankful for the support from the Lisboa 2020 Programme, Centro 2020 Programme, Portugal 2020, European Union, through the European Social Fund which supported LISBOA-05-3559-FSE-000007 and CENTRO-04-3559-FSE-000094 operations as well as Fundação para a Ciência e Tecnologia (FCT) and Agência Nacional de Inovação (ANI). The NMR spectrometers are part of the National NMR Network (PTNMR) which is partially supported by the Infrastructure Project No. 022161 (co-financed by FEDER through COMPETE 2020, POCI and PORL and FCT through PIDDAC).

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