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Ammonium Acetate Catalyzed Formation of 1,5-Benzodiazepines through [4+2+1] Cycloaddition Involving 5-Hydroxymethylfurfural

Jingjing Jiang,^[a] Dr. Yves Queneau^{[a]*} and Prof. Dr. Florence Popowycz^{[a]*}

[a] Université de Lyon, INSA Lyon, Université Lyon 1, CNRS, CPE, UMR 5246, ICBMS, 1 rue Victor Grignard, F-69621 Villeurbanne Cedex

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Abstract: The use of the renewable platform molecule 5-hydroxymethylfurfural (5-HMF) in multi-component reaction with a diamine and an alkyne to generate seven-membered 1,5-benzodiazepines is described. Due to the sensitivity of 5-HMF to strong acidic and basic conditions, the investigation required an in-depth revisit of reaction parameters as compared to benchmark aldehydes. Among catalysts/solvents couples, ammonium acetate in ethanol proved to be a clean and efficient system. These optimized conditions were subsequently used to investigate the scope of the reaction providing a library of 1,5-benzodiazepines in moderate to good yield from a wide range of diversely substituted diamines and alkynes or alkyl alkynoates.

Introduction

Against the background of developing more sustainable chemical methods, one among many directions is to replace raw materials arising from fossil resources with greener, renewable ones while also meeting the characteristics of generality and abundance. Considered as the most abundant renewable carbon resource in nature, biomass has attracted significant attention from both academia and industry.^[1-3] Biomass and its derivatives can produce high-quality bio-based fuels and bulk chemicals through appropriate conditions.^[4,5] The structural diversity found in renewable resources is also an opportunity for reaching a wide range of chemical groups found in functional materials and fine chemicals.^[6,7] Widening the scope of biomass-derived molecules used in fine chemistry can gradually reduce people's dependence on fossil resources, and also provide opportunities for the development of a more sustainable organic chemistry. As a promising bio-based platform molecule, 5-HMF can be produced by dehydration of glucose or fructose extracted from agricultural and forestry biomass. 5-HMF is considered to be an important building block due to its rich chemical reactivity and its ready availability from sugars. The diversification of 5-HMF chemistry towards fine chemicals is a rapidly developing topic and it is increasingly used in the synthesis of polymer monomers and other high value-added chemicals and even some pharmaceutical intermediates.^[8-15]

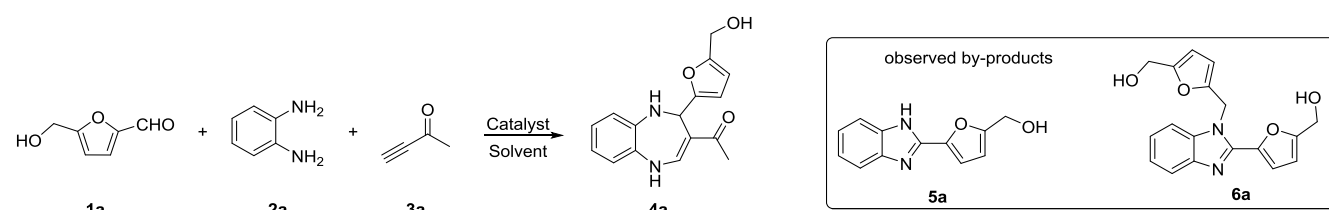
Nitrogen-containing heterocycles are widely dispersed in natural products and pharmaceutical products, owing to their unique pharmacological activities.^[16] As a representative nitrogen-containing heterocyclic compound, 1,5-benzodiazepine skeletons are widely used in biological and pharmaceutical fields due to their biological and pharmacological activities or as intermediates.^[17-21] Therefore, the development of efficient methods for the synthesis the 1,5-benzodiazepine scaffold from simple substrates is highly desirable. Coupling of diamines with α,β -unsaturated ketones, β -diketones, β -keto esters and aliphatic ketones in the presence of catalysts is the most common method for the synthesis of 1,5-benzodiazepines. In recent years, some methods for the synthesis of 1,5-benzodiazepines through multi-component reactions with simple raw materials have been gradually developed. Considered as commonly used synthons in organic synthesis, the multi-component reactions using aldehydes to construct 1,5-benzodiazepines have been reported many times. In addition, various Lewis acids, Brønsted acids, supported catalysts and nano-catalysts have been demonstrated as good mediators to successfully promote the formation of 1,5-benzodiazepines in different multi-component reactions involving aldehydes.^[22,23] For example, in 2016, Wang et al. discovered a Lewis acid-catalyzed chemo-/regio-selective synthesis of 1,5-benzodiazepines using an *o*-phenylenediamine, an aromatic aldehyde and a but-3-yn-2-one as raw materials.^[24] Regarding the scope of aldehydes, while the use of benzaldehydes, heterocyclic and aliphatic aldehydes toward 1,5-benzodiazepines has been intensively explored, there are no reports involving 5-HMF in such reactions. The combination of its three characteristics (furan ring, aldehyde and hydroxymethyl group) which makes its chemical richness is however a limitation in such an acid-catalyzed multicomponent processes as compared to furfural for example, and reports on multi-component reactions of 5-HMF are sparse until now^[25-32] but show that it is possible to define suitable conditions that preserved its stability. In keeping with this strategy, we herein report the results of a detailed methodological investigation of the [4+2+1] cycloaddition reaction of 5-HMF with *o*-phenylenediamine and but-3-yn-2-one parameters targeting the 1,5-benzodiazepine scaffold. The study focuses first on the search for the most appropriate catalyst-solvent couple, before evaluating the structural scope of the reaction using diversely substituted diamines and alkynes or alkyl alkynoates.

Results and Discussion

We initiated our study by identifying the products arising from the three-component reaction of 5-hydroxymethylfurfural (**1a**), *o*-phenylenediamine (**2a**) and but-3-yn-2-one (**3a**) in ethanol in the absence of any catalyst. The reaction was performed in a sealed tube at 60°C using the stoichiometry ratio in **1a** (1.2 equiv.), **2a** (1.0 equiv.) and **3a** (1.0 equiv.) (Table 1, entry 1). In this reaction, the desired seven-membered 1,5-benzodiazepine **4a** was obtained in 34% yield (measured by ¹H NMR spectroscopy of the crude mixture

using 1,3,5-trimethoxybenzene as internal standard). Besides, [5-(1*H*-benzo[d]imidazol-2-yl)furan-2-yl]methanol **5a** and {5-([2-[5-(hydroxymethyl)furan-2-yl]-1*H*-benzo[d]imidazol-1-yl)methyl]furan-2-yl)methanol **6a** were produced in 8 % and 18 % yield respectively, which may arise from the condensation/cyclization sequence of 5-HMF and *o*-phenylenediamine (see the SI for detailed characterization of all products). Looking for more selective conditions toward **4a**, we screened more than twenty catalysts including Lewis acids, Brønsted acids and some bases. However, addition of catalytic amounts of Lewis acids such as FeCl₃, AlCl₃, ZnCl₂ and I₂ significantly inhibited this transformation although 5-HMF was completely consumed, while CsBr provided similar yields to those under catalyst-free condition. *p*-Toluenesulfonic acid, acetic acid or benzoic acid did not provide better results, consistently with known HMF instability in the presence of Brønsted acids (Table 1, entries 2-9), resulting in a complex mixture of products with low yield of the expected compound **4a**. Overall, routinely used Lewis and Brønsted acids were not suitable for this reaction (see the complete list of screened catalysts in SI). Subsequently, several ammonium-containing catalysts were screened for this reaction. Ammonium acetate and ammonium sulfate have been shown to promote glucose dehydration to 5-HMF with good yields, suggesting limited acid-catalyzed degradation compared to harsher acids.^[33] Applied to the reaction of 5-HMF, *o*-phenylenediamine (**2a**) and but-3-yn-2-one (**3a**), the presence of ammonium salts such as NH₄OAc, NH₄HCO₂, (NH₄)₂CO₃ and (NH₄)₂SO₄ reduced by-product **6a** from 18% to trace amounts, which also facilitated easier separation of the products (Table 1, entries 10-13). Among the various ammonium salts investigated, NH₄OAc exhibited the best efficiency by a small margin with 68% NMR yield (70 % isolated yield) of the desired product **4a** (Table 1, entry 10). Running the same reaction with different load of catalysts did not offer better results than the 30 mol% amount which was thus used in the next experiments (catalyst loading comparisons are provided in SI). With respect to the solvent, ethanol gave clearly the best results as compared to a collection of organic solvents such as MeCN, DCM, THF, 1,4-dioxane, DMSO or water (Table 1, entries 14-19). Finally, performing the reaction at 50°C or 80°C led to a decrease in the yield (Table 1, entries 20-21).

Table 1. Optimization of the reaction conditions.^[a]

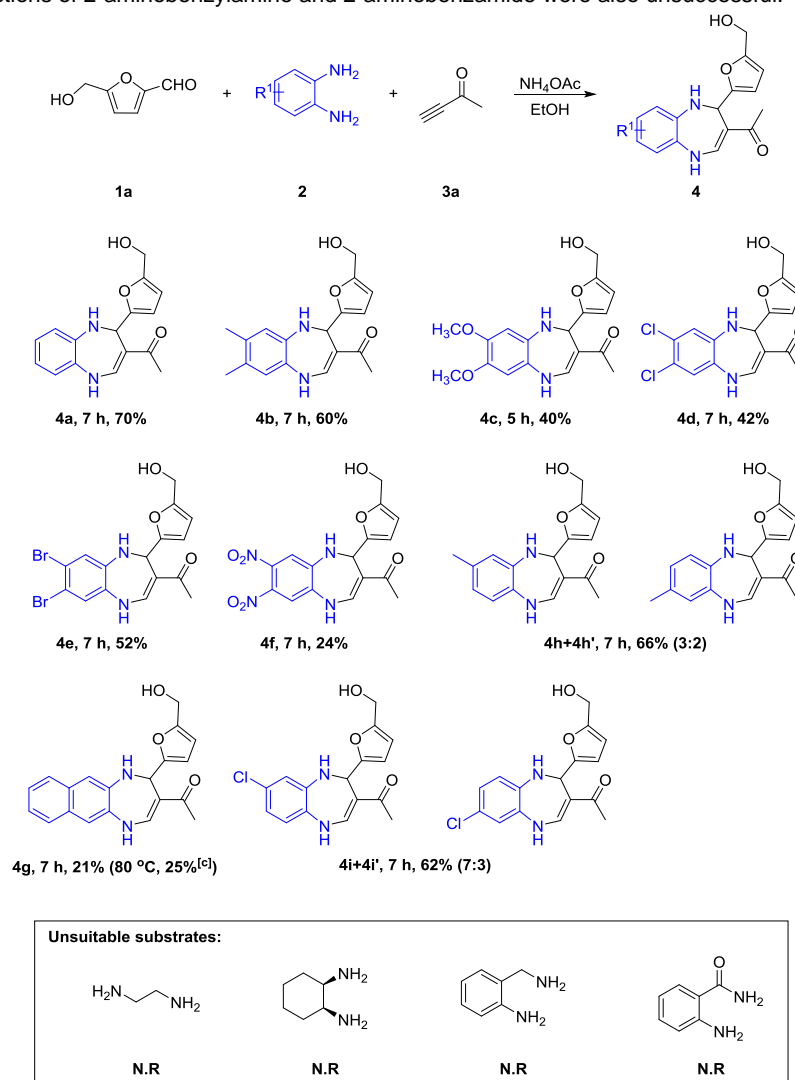


Entry	Catalyst	Temperature	Time	Solvent	NMR Yield of 4a/5a/6a ^[b]
1	---	80 °C	16 h	EtOH	34/8/18
2	FeCl ₃	80 °C	16 h	EtOH	2/9/23
3	AlCl ₃	80 °C	16 h	EtOH	trace/5/14
4	ZnCl ₂	80 °C	16 h	EtOH	10/9/14
5	I ₂	80 °C	16 h	EtOH	2/0/22
6	CsBr	80 °C	16 h	EtOH	38/8/17
7	PTSA	80 °C	16 h	EtOH	36/trace/17
8	CH ₃ COOH	80 °C	16 h	EtOH	32/trace/22
9	PhCOOH	80 °C	16 h	EtOH	30/trace/27
10	NH₄OAc	60 °C	7 h	EtOH	68/14/trace (70) ^[c]
11	NH ₄ HCO ₂	60 °C	6 h	EtOH	60/12/trace
12	(NH ₄) ₂ CO ₃	60 °C	6 h	EtOH	43/8/trace
13	(NH ₄) ₂ SO ₄	60 °C	6 h	EtOH	66/10/trace
14	NH ₄ OAc	60 °C	7 h	MeCN	31/27/trace
15	NH ₄ OAc	60 °C	7 h	DCM	52/13/trace
16	NH ₄ OAc	60 °C	7 h	THF	13/messy
17	NH ₄ OAc	60 °C	7 h	1,4-Dioxane	26/messy
18	NH ₄ OAc	60 °C	7 h	DMSO	23/messy
19	NH ₄ OAc	60 °C	7 h	H ₂ O	19/7/trace
20	NH ₄ OAc	50 °C	7 h	EtOH	60/14/trace
21	NH ₄ OAc	80 °C	7 h	EtOH	56/14/trace

[a] Reaction conditions: **1a** (1.2 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), catalyst (30 mol%), solvent (2.0 mL), 60 °C, sealed tube. [b] ¹H NMR yield based on **2a/3a**. [c] Isolated yield of **4a** [%].

The optimized conditions (30 mol% NH₄OAc in ethanol, 60°C, sealed tube), which generated compound **4a** in 70% isolated yield were then used throughout the exploration of the substrate structural scope. Firstly, a collection of variously substituted *o*-phenylenediamines were used in the reaction (Scheme 1). In general, all *o*-phenylenediamines reacted smoothly to afford the corresponding

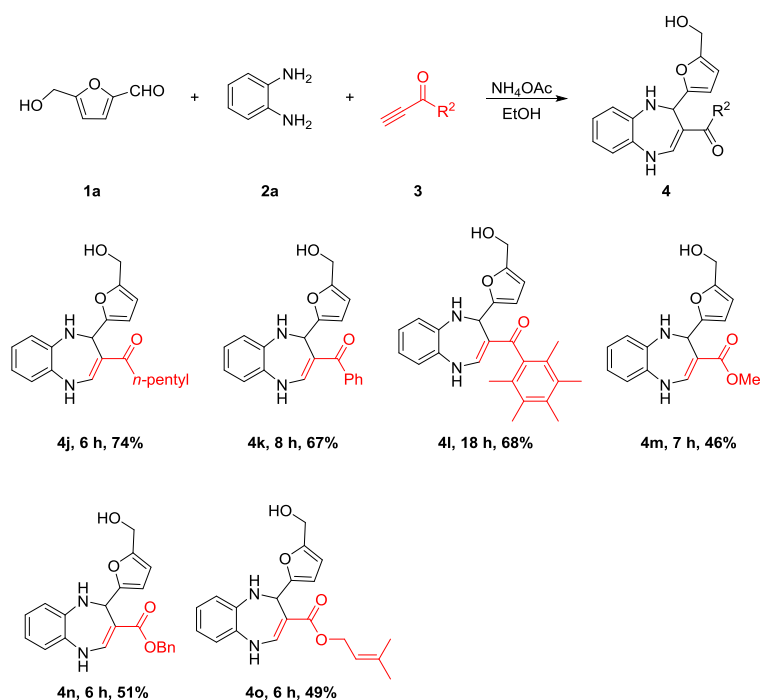
1,5-benzodiazepines in fair yields with a good tolerance of functionalities such as alkyl, alkoxy and halo substituents. The six substituted but symmetrical *o*-phenylenediamines conducted logically to a single product (**4b-4g**). The reaction yield significantly decreased to 24% when 4,5-dinitrobenzene-1,2-diamine was tested (**4f**) due to the presence of the strong electron-withdrawing substituent NO₂ group. Non-symmetrical *o*-phenylenediamines led to a mixture of two regioisomers difficult to separate (**4h/h'** and **4i/i'**) but in the same range of yield (66% and 62% respectively). Unfortunately, other symmetric diamines such as ethylenediamine and *cis*-1,2-cyclohexanediamine are not appropriate substrates for this transformation and only trace amounts of the target product can be detected by GC-MS. Reactions of 2-aminobenzylamine and 2-aminobenzamide were also unsuccessful.



[a] Reaction conditions: 5-HMF (**1a**, 1.2 mmol), *o*-phenylenediamines (**2**, 1.0 mmol), but-3-yn-2-one (**3a**, 1.0 mmol) and NH₄OAc (30 mol%) in EtOH (2.0 mL), stirred at 60 °C for indicated time. [b] Isolated yield unless otherwise stated. [c] ¹H NMR yield.

Scheme 1. Synthesis of 1,5-benzodiazepines from 5-HMF, but-3-yn-2-one and various *o*-phenylenediamines. ^{[a][b][c]}

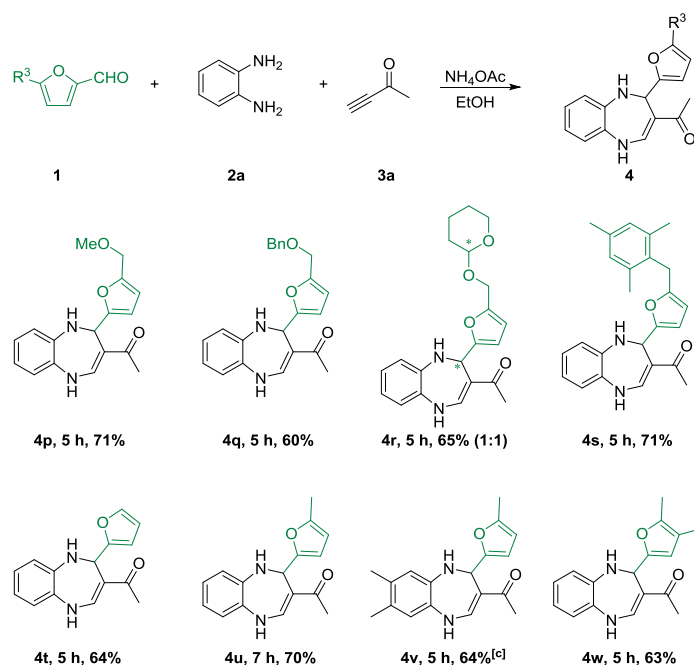
The scope investigation was then extended to the alkyne reagent, using commercially available or easily prepared^[34-37] alkynes or alkyl alkynoates (Scheme 2). Good yields of desired product were obtained when 1-octyn-3-one or 1-phenylprop-2-yn-1-one were used as reagents, giving the products **4j** and **4k** in 74% and 67% yields, respectively. Reaction with 1-(2,3,4,5,6-pentamethylphenyl)prop-2-yn-1-one required an extended reaction time to 18 hours for yielding product **4l** in 68% yield. Alkyl propynoates exhibited lower reactivity in their reaction with 5-HMF and *o*-phenylenediamine, with 1,5-benzodiazepines yields from 46% to 51% (**4m-4o**), consistently with a lower electron withdrawing effect compared with ketones.



[a] Reaction conditions: 5-HMF (**1a**, 1.2 mmol), o-phenylenediamine (**2a**, 1.0 mmol), alkynes and alkyl alkynoates (**3**, 1.0 mmol) and NH₄OAc (30 mol%) in EtOH (2.0 mL), stirred at 60 °C for indicated time. [b] Isolated yield.

Scheme 2. Synthesis of 1,5-benzodiazepines from 5-HMF, o-phenylenediamine and various alkynes and alkyl alkynoates.^{[a][b]}

After screening various diamines and alkynes/alkyl alkynoates for this three-component procedure, a series of substituted furfural was investigated (Scheme 3). First, several 5-HMF-derived substrates, prepared from 5-HMF through known procedures^[38-41] react smoothly under the optimized conditions affording the target products with yields of 71% (**4p**), 60% (**4q**), 65% (**4r**, as a (1:1) mixture of two diastereomers), and 71% (**4s**), respectively. Furfural and commercially available 5-methylfurfural and 4,5-dimethyl furfural can also react well to give the desired products in the same range of yields (63% to 70%) (**4t-4w**).

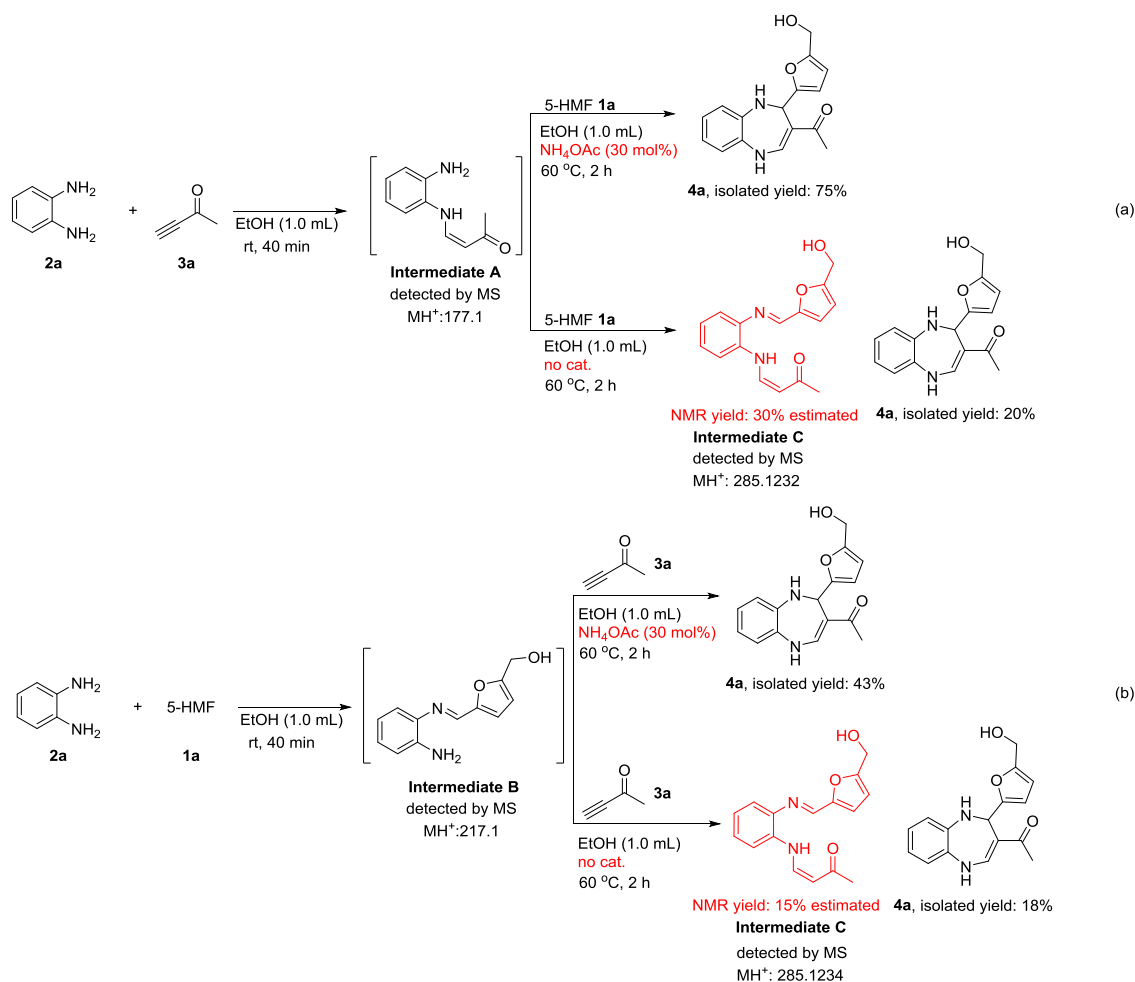


[a] Reaction conditions: aldehyde compounds (**1**, 1.2 mmol), o-phenylenediamine (**2a**, 1.0 mmol), but-3-yn-2-one (**3a**, 1.0 mmol) and NH₄OAc (30 mol%) in EtOH (2.0 mL), stirred at 60 °C for indicated time. [b] Isolated yield. [c] from 4,5-dimethyl-1,2-phenylenediamine (**2b**, 1.0 mmol).

Scheme 3. Synthesis of 1,5-benzodiazepines from variously substituted furfural, o-phenylenediamine and but-3-yn-2-one.^{[a][b][c]}

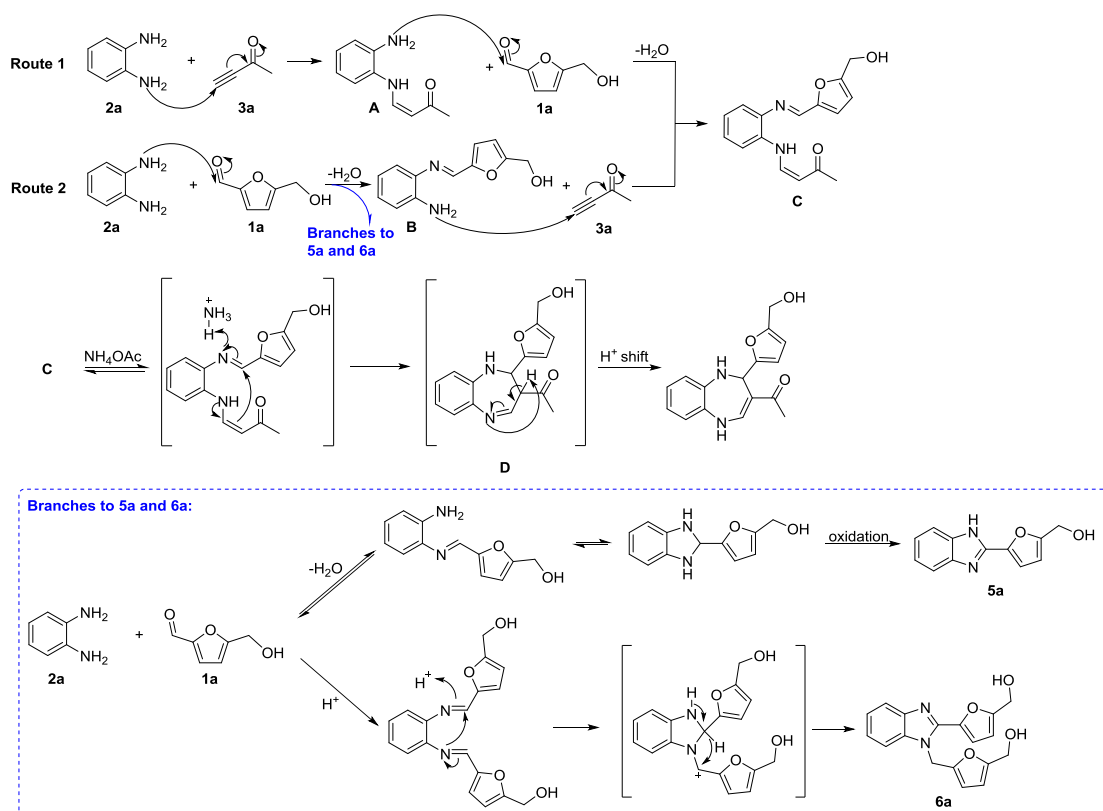
In multi-component reactions, the reaction may undergo different pathways due to the interaction between different reactants. Aiming at a better understanding of the mechanism in the present case, control experiments were conducted in the presence of two partners amongst the three, with attempts to detect reaction intermediates by NMR or mass spectrometry (MS) experiments, before adding the

third partner (Scheme 4). When mixing *o*-phenylenediamine and but-3-yn-2-one in ethanol for 40 minutes at room temperature, the enamine product **A** can be detected by MS (enamine plus H⁺: 177.1). Then, 5-HMF, ammonium acetate and ethanol (1 mL) were added to the solution and stirred at 60°C for 2 hours to obtain **4a** with an isolated yield of 75% (Scheme 4, a). When this second step was performed without ammonium acetate, only 20% of **4a** was obtained after 2 hours, together with a 30% estimated yield (NMR) of the uncyclized intermediate **C** (see the SI for detailed characterization of intermediate C), identified by HRMS with a MH⁺ 285.1232. The other way round was to mix *o*-phenylenediamine and 5-HMF, leading to the imine product **B** detected by MS (imine plus H⁺: 217.1), before but-3-yn-2-one and ammonium acetate were added, yielding the target product in a lower 43% yield (Scheme 4, b). Formation of intermediate **C** (MH⁺: 285.1234) was also observed when the second step was performed in absence of any catalyst.



Scheme 4. Control experiments.

On the basis of the above experimental observations and previous reports, a possible reaction mechanism is proposed (Scheme 5). The reaction may first generate intermediate enaminoketone **A** through the addition of **2a** and **3a**, then intermediate **C** by formation of an imine arising from the reaction of the second amino group of **2a** with the carbonyl group of 5-HMF (Scheme 5, route 1). The alternative route is the formation of the imine intermediate **B** by condensation of one amino group of *o*-phenylenediamine with 5-HMF, then reaching intermediate **C** by 1,4-addition of the second amino group onto the alkyne **3a** (Scheme 5, route 2). Ammonium acetate could promote the intramolecular cyclization of intermediate **C** into intermediate **D**, which would undergo a proton transfer to form the more stable target product. It is also possible that ammonium acetate would activate the ketone to more reactive intermediates, either by protonation or by formation of an iminium, facilitating subsequent ring formation. As route 2 explains that the reaction can diverge towards by-products **5a** and **6a** and taking into account the compared yields in the counter experiments, the reaction likely proceeds through a mixed pathway.



Scheme 5. Possible mechanism.

Conclusion

In summary, we have reported the first application of bio-based 5-HMF in multi-component reaction to construct 1,5-benzodiazepines, thanks to the application of a set of mild reaction conditions (ammonium acetate in ethanol). This reaction, which was found to be applicable to a broad range of substrates, provides a facile and efficient entry to functionalized 1,5-benzodiazepines. Furthermore, this reaction provides a diversification of the scope of fine chemicals arising from 5-HMF. In terms of mechanism, the participation of ammonium ions is considered to be the key to improve chemoselectivity, offering an interesting, mild and clean alternative method for broadening the functionalization of 1,5-benzodiazepines. Investigations on the detailed mechanism and further applications are in progress in our laboratory.

Experimental Section

Reagents and solvents were supplied by Aldrich, Acros, Lancaster, Alfa Aesar, Fluka, Carlo Erba or TCI and purchased at the highest commercial quality to be used without further purification, unless otherwise stated in the procedure. NMR spectra were recorded on a Bruker DRX-300 (1H : 300 or 400 MHz; ^{13}C : 75 or 100 MHz) spectrometer using $DMSO-d_6$. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a Thermo Finnigan LCQ Advantage mass. High-resolution mass spectra (HRMS) were recorded on Bruker MicrOTOF-Q II XL spectrometer using ESI as ionization source. Analytical thin-layer chromatography was carried out on silica gel Merck 60 D254 (0.25 mm). Flash chromatographies were performed on Merck Si 60 silica gel (40–63 μm).

General procedure: A solution of aldehydes (1.2 mmol, 1.2 equiv.), o-phenylenediamines (1.0 mmol, 1.0 equiv.), alkynes or alkyl alkynoates (1.0 mmol, 1 equiv.), NH_4OAc (23 mg, 30 mol%) in ethanol (2 mL) was stirred at 60°C for 5-18 hours. After cooling down to room temperature, the reaction was diluted with ethyl acetate (20 mL) and washed with saturated aqueous sodium chloride solution (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x10 mL). The organic phases were combined and dried over Na_2SO_4 . After filtration, the residue was concentrated and purified by flash column chromatography on silica gel (*n*-pentane/EA=3:7 to 0:10) or (DCM/MeOH=80:1 to 10:1).

Acknowledgements

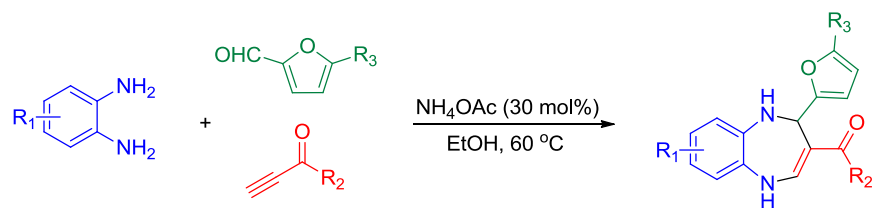
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Keywords: 1,5-benzodiazepines, ammonium acetate, 5-HMF, MCR, cycloaddition, metal-free

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Table of Contents Entry



23 examples, up to 74% yield

- ✓ *One-pot MCR strategy, clean solvent, mild and new catalyst*
- ✓ *First access to 1,5-benzodiazepines involving 5-HMF*

Ammonium acetate in ethanol is a clean and efficient protocol for the multi-component construction of 1,5-benzodiazepines, being an appropriately mild catalyst in the case of the acid-sensitive biobased platform 5-hydroxymethylfurfural (5-HMF). The protocol is tolerant to many functional groups in substituted diamines, alkynes or alkyl alkynoates, and furanic aldehydes.