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Searching for novel reusable biomass-derived solvents: furfuryl alcohol/water azeotrope as medium for the waste-minimised copper-catalysed azide-alkyne cycloaddition†

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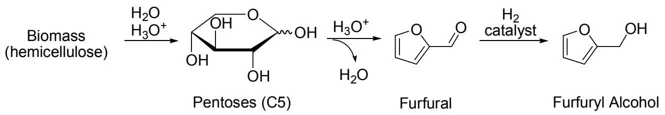
Herein, we report the first application of the furfuryl alcohol/water azeotrope as a sustainable and easily recoverable reaction medium in organic chemistry. The applicability of this novel medium was tested in the copper-catalysed azide-alkyne cycloaddition (CuAAC), a reaction usually conducted in mixtures of water and an organic solvent. Our reaction conditions allowed isolating the expected triazoles in generally good yields and usually in shorter times compared to classical reaction conditions, also proving a wide substrate scope. A large fraction of the furfuryl alcohol/water azeotrope can be recovered by simple distillation at the end of the reaction, which results in a dramatic decrease in waste production and E-factors, compared to typically employed CuAAC procedures.

Introduction

The vast majority of the chemicals and fuel produced nowadays comes from fossil non-renewable resources. On a large scale, the replacement of these materials with alternatives deriving from renewable resources is a high priority in order to establish a more modern and competitive and sustainable chemical production. Biomass represents the only renewable source of carbon,[1-4] and it has been estimated that 25-30% of chemical commodities will be generated from biomass by 2030.[2-4] In this perspective, large attention is currently devoted to finding alternative platform chemicals deriving from renewable biomass resources[5] that could be used, directly or after modifications, as fuels or for the production of value-added chemicals and materials.[6,7]

It has been calculated that most of the waste generation associated to organic syntheses, particularly in pharmaceutical industries, comes from the use of solvents.[8] Moreover, life cycle assessments have also confirmed that solvents account for the majority of the environmental footprint in the production of key areas such as the pharmaceutical industry.[9] It is therefore not surprising that chemical industries are increasingly concerned about their choices in the use of solvents.[10] The replacement of commonly employed solvents, which almost entirely derive from fossil resources, with alternative reaction media that could be easily produced from biomass would represent a major advancement in terms of sustainability for the chemical industry.[11] An interesting and representative example of a biomass-derived chemical which has recently come to attention as a possible substitute for traditional solvents is γ-valerolactone (GVL).[12,13] GVL is typically produced by hydrogenation of lignocellulosic biomass-derived levulinic acid[14,15] and, due to its physical-chemical properties, represents an ideal replacement for dipolar aprotic solvents (e.g. dimethylformamide, *N*-methyl-2-pyrrolidone), whose use is now strictly regulated because of their toxicity.[16]

We have also been searching for other biomass-derived chemicals that could find potential application as a reaction medium in chemical processes, and we individuated furfuryl alcohol (FA) as a very interesting candidate. FA is manufactured by hydrogenation of furfural, one of the products deriving from degradation of hemicellulose (Scheme 1),[17] and has found its main application in the synthesis of resins and as intermediate in organic syntheses.[18]



Scheme 1. Reaction pathway for furfuryl alcohol production from biomass.

FA is a clear liquid that, as typical of alcohols, is miscible with water and several organic solvents (e.g. acetone, ethylacetate, benzene, chloroform).

A desirable feature for a sustainable reaction medium is the possibility for it to be easily recovered at the end of the process and reused. This would in fact dramatically reduce its environmental impact. Pure FA has a relatively high boiling point of 171 ºC, which would compromise its possible recovery

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or, at least, make it very energetically demanding.[10b] However, very interestingly, it forms an azeotrope with water (20 wt% of FA) that boils at 98.5 ºC, which is a reasonable temperature for distillation.

The use of homogeneous mixtures of an organic solvent and water as reaction medium is very common in organic chemistry, mainly to ease the dissolution of both organic and inorganic reagents, as well as inorganic additives and/or catalyst. These organic solvent/water mixtures are used in ratios that are generally suggested by practical tradition and cannot be easily recovered and reused, therefore producing waste. At this concern, we have developed several protocols based on the use of safer media and solid catalytic systems[19] and proposed that aqueous azeotropes can be a very effective solution, combining the benefits of aqueous solvents with being easily recoverable and reusable.[20]

In this perspective, we reasoned that the FA/water azeotrope could represent a sustainable and recoverable alternative to commonly used mixtures of water and an organic solvent. Here we should mention that, to the best of our knowledge, FA or the FA/water azeotrope have never been used as reaction media in organic chemistry applications.

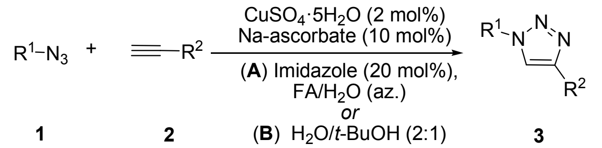
In order to verify our hypothesis we decided to test the FA/water azeotrope as medium in one of the most widely applied reactions in organic synthesis which is typically performed in aqueous/organic mixtures: the copper-catalysed azide-alkyne cycloaddition (CuAAC).[21] As a typical *click* reaction, CuAAC is a very robust reaction and normally proceeds in mild conditions, ambient temperature, with low catalyst loading, in different pH values and gives products in high yields with minimal work up. Applications of CuAAC for the preparation of materials of interest in different areas is countless.[22]

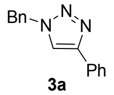
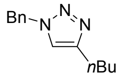
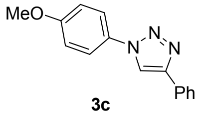
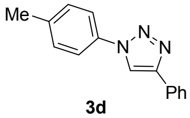
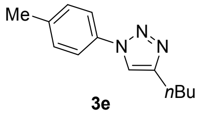
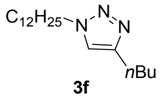
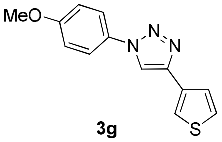
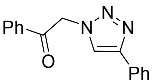
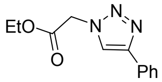
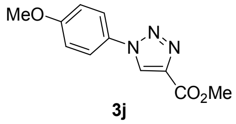
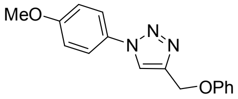
Classical CuAAC is performed by *in situ* generation of Cu(I) from Cu(II) salts ($CuSO_4$ or $Cu(OAc)_2$) using sodium ascorbate or ascorbic acid as reductant in water media with organic co-solvents such as alcohols (*t*-BuOH, EtOH, MeOH), DMSO, acetonitrile, THF or CH_2Cl_2. Cu(I) salts can also be used directly, but this typically requires inert atmosphere to prevent oxidation. Addition of an organic base (2,6-lutidine, Et_3N, imidazoles, DIPEA or pyridine) or different ligands can stabilize Cu(I), reduce reaction times and improve reaction yields.[23] Recently, considerable attention has turned to green chemistry approaches for CuAAC and immobilized Cu-catalysts,[24] solvent-free conditions[25] and reactions in flow[26] have been reported.

Results and discussion

We started our investigation by testing the FA/water azeotrope as reaction medium for the synthesis of 1,4-disubstituted-1,2,3-triazoles from azides and alkynes (Table 1).

Table 1. Copper-Catalysed Azide-Alkyne Cycloaddition[a]



Entry	Product	Solvent system	Time (h)	Conv. (%)[b]
1	 **3a**	**A** **B**	6 24	100 (68)[c] 66
2	 **3b**	**A** **B**	3 24	100 (79)[d] 99
3	 **3c**	**A** **B**	24 24	100 (59)[c] 84
4	 **3d**	**A** **B**	6 24	100 (87)[c] 100
5	 **3e**	**A**	24	100 (81)[d]
6	 **3f**	**A**	24	98 (81)[c]
7	 **3g**	**A**	6	98 (87)[c]
8	 **3h**	**A** **B**	3 3	100 (95)[c] 100
9	 **3i**	**A**	6	100 (80)[c]
10	 **3j**	**A**	3	100 (91)[c]
11	 **3k**	**A**	24	100 (91)[c]

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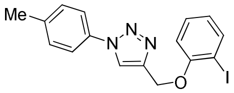
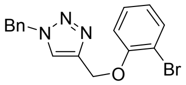
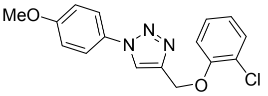
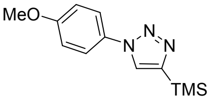
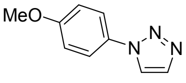
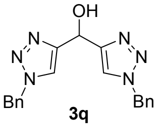
12	 **3l**	**A**	6	100 (93)[c]
13	 **3m**	**A**	3	100 (86)[d]
14	 **3n**	**A**	3	100 (84)[c]
15	 **3o**	**A**	3	95 (68)[e]
16[f]	 **3p**	**A**	24	100 (67)[e]
17	 **3q**	**A**	3	100 (82)[c]

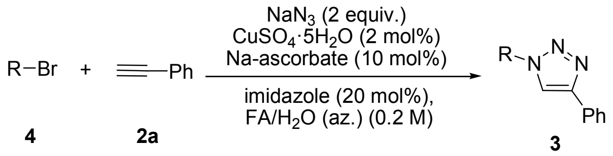
[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), $CuSO_4{\cdot}5H_2O$ (2 mol%), Na-ascorbate (10 mol%), (**A**) 5 mL FA/H_2O (20 wt%), imidazole (20 mol%); (**B**) 5 mL *t*-BuOH/H_2O (1:2). [b] Conversion of **1** and **2** to **3** determined by GC analysis using 4-bromoanisole as internal standard; isolated yields in parentheses. [c] Product is solid in the reaction medium and was isolated by filtration. [d] Product is a oil in the reaction medium and was isolated by decantation of the azeotrope, addition of water to precipitate the product and filtration. [e] Product is a oil in the reaction medium and was isolated by EtOAc/water work-up and subsequent column chromatography. [f] Prepared from trimethylsilylacetylene; TBAF (2 equiv.) was added after consumption of starting materials (3h) and the mixture was stirred for additional 21h at 30 ºC.

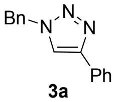
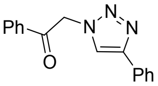
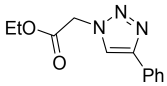
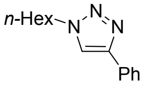
As catalyst we used what is probably the most commonly employed system in CuAAC reactions: 2 mol% $CuSO_4{\cdot}5H_2O$ and 10 mol% sodium ascorbate. In several cases, for the sake of comparison, we also conducted the reaction in the representative water/*t*-BuOH (2:1) mixture, which is commonly used in CuAAC reactions. When using FA/water azeotrope we found optimal results by adding as ligand a catalytic amount of imidazole (20 mol%).[27]

Reactions in FA/H_2O azeotrope achieve full conversion in 3–24 h, and usually the reaction time is shorter compared to the same reaction conducted in *t*-BuOH/water (1:2) (Table 1, entries 1, 2 and 4). These results can be ascribed to the apparently lower solubility of the products and substrates in FA/H_2O azeotropes in comparison with *t*-BuOH/water (1:2). With adequate stirring, this determines a beneficial effect for both reactions giving solid or oily products. Further investigations are ongoing to deeper understand this phenomenon.

Substrate scope is quite general, with both alkyl and aryl azides and alkynes affording the corresponding products in yields ranging from good to excellent. Various substituents such as thiophenyl (entry 7), ketone (entry 8) and aromatic halides (entries 12-14) are compatible with the reaction conditions, and the related products are selectively formed without observable side-products formation. Ester functionalities are also tolerated and no transesterification with FA was observed (entries 9 and 10). Interestingly, trimethylsilylacetylene gives TMS-containing triazole **3o** as major product (entry 15), with a limited (less than 10 %) formation of the mono-substituted triazole **3p**, as detected by GC analysis.[28] However, product **3p** can be obtained by adding TBAF to the reaction mixture after 3 hours and stirring at 30 ºC for additional 21 hours (entry 16). Moreover, our method allows the preparation in good yields of bis-triazoles (entry 17), a class of compounds that has found applications in different fields.[29]

Table 2. Preparation of 1,4-disbutituted-1,2,3-triazoles from alkylbromides[a]



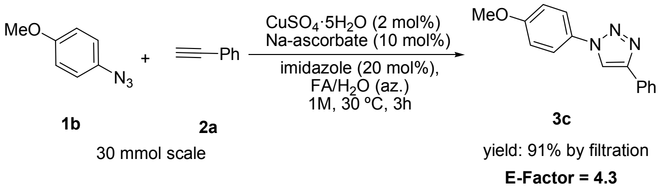
Entry	Product	Temperature (ºC)	Time (h)	Conv. (%)[b]
1	 **3a**	30	3	100 (92)[c]
2	 **3h**	30	3	100 (94)[c]
3	 **3i**	30	18	100 (87)[c]
4	 **3r**	60	48	89 (53)[d]

[a] Reaction conditions: **4** (1 mmol), **2a** (1 mmol), $CuSO_4{\cdot}5H_2O$ (2 mol%), Na-ascorbate (10 mol%), imidazole (20 mol%), NaN_3 (2 mmol), 5 mL FA/H_2O (20 wt%). [b] Conversion of **1** and **2** to **3** determined by GC analysis using 4-bromoanisole as internal standard; isolated yields in parentheses. [c] Product is solid in the reaction medium and was isolated by filtration. [d] Product is solid in the reaction medium and was isolated by filtration and washed with water and hexane to remove unreacted starting materials.

For the isolation of the products **3**, we have defined two general methods. First, if the product precipitated in the reaction medium, simple filtration followed by washing of the solid with water was sufficient to obtain pure products. Otherwise, when the product was oil in the reaction medium the solvent mixture was removed by decantation and water was added to precipitate the product. In almost all the cases products were pure and no additional purification was required, with triazoles **3o** and **3p** being the only exceptions.

It is known that CuAAC reactions can also be conducted with the *in situ* formation of the organic azide starting from a corresponding alkyl halide and sodium azide.[24a,30] To test whether this possibility is also applicable in the FA/water azeotrope, we reacted alkyl bromides (**4**) with phenylacetylene **2a** and 2 equivalents of sodium azide in the presence of the previously used catalytic system (Table 2). To our delight benzyl bromide, 2-bromoacetophenone and ethyl bromoacetate reacted smoothly and the corresponding triazoles **3a**, **3h** and **3i** were isolated in 87-94% yields (Table 2, entries 1-3). Unfortunately, the less reactive hexyl bromide gave low conversion at 30 ºC. Higher temperature (60 ºC) and longer reaction time (48 h) were required to achieve 89 % conversion to 1-hexyl-4-phenyl-1H-1,2,3-triazole **3r** (Table 2, entry 4). Isolated yield was moderate (53 %), since additional washing of the solid product with hexane was necessary in order to remove unreacted starting materials.

Finally, to test the recoverability of the reaction medium, we performed the representative reaction between 4-azidoanisole **1b** and phenylacetylene **2a** on a 30 mmol scale, in our standard reaction conditions but at higher concentration (Scheme 2).



Scheme 2. CuAAC Reaction on a 30 mmol scale.

In these conditions the isolated yield of product **3c** could be considerably improved, from 59% to 91%, mainly as a consequence of easier product isolation at a larger scale. At the end of the process the FA/water azeotrope was distilled, allowing the recovery of 21 g (81% of the initial amount, this result can be certainly further optimized) of the mixture. NMR analysis confirmed the purity of the recovered azeotrope, which could be reused for subsequent reactions. We have reused the same recovered azeotropes for three consecutive runs without observing any change in the ratio of the mixture.

To assess the greenness of our procedure we calculated the E-factor[31] of our large scale reaction (Scheme 2), obtaining a value of 4.3. As a comparison we also calculated the E-factors for some typical CuAAC procedures. Usually these reactions are performed in water and an organic co-solvent, and the recovery of the resulting mixture is practically not possible. In our analysis we considered: i) the classical procedures reported by Sharpless and Fokin using *t*-BuOH/water,[21c] ii) a procedure using CH_2Cl_2/H_2O as reaction medium[32] and, iii) a solvent-free reaction.[25a] Even if in our calculation we neglected the fact that typically these procedures require product purification by column chromatography, still we calculated an average E-factor of 106. Thus, our method leads to a significantly (96%) smaller production of waste compared to classical CuAAC procedures. This is not surprising, since this confirms mathematically that solvents represent the largest mass of the chemicals employed and therefore the definition of a protocol for their recovery and reuse is fundamental for the minimisation of waste in synthetic processes.

Conclusions

In conclusion we reported what, to the best of our knowledge, is the first application of biomass-derived furfuryl alcohol as a reaction medium in organic chemistry. Using the FA/water azeotrope instead of pure FA, the reaction mixture is easily recoverable by simple distillation. The applicability of the FA/water mixture as reaction medium was tested in the copper-catalysed azide-alkyne cycloaddition, a reaction often performed in mixtures of water and an organic solvent. Our reaction conditions lead to the selective formation of the expected triazoles in good to excellent yields, often in shorter times compared to the reactions conducted in *t*-BuOH/water. Moreover, a wide substrate scope was demonstrated, with different functional groups being tolerated in our reaction conditions. Finally, the use of the FA/water azeotrope lead to a considerable reduction in waste generation compared to classical CuAAC procedures, as proven by the dramatic reduction in the E-factor values.

We believe that the FA/water azeotrope can represent a sustainable and chemically efficient alternative reaction medium, especially for reactions that work best in mixtures of water and an organic solvent. Further investigations in this perspective are currently ongoing in our laboratories.

Experimental

General procedure for the synthesis of 1,5-disubstituted 1,2,3-triazoles

Imidazole (14 mg, 20 mol%), sodium ascorbate (20 mg, 10 mol%) and copper(II) sulfate pentahydrate (5 mg, 2 mol%) were dissolved in 5 mL of furfuryl alcohol (20 wt%) water mixture, in a screw-capped vial equipped with a magnetic stirrer. Alkyne (1 mmol) and azide (1 mmol) were added and the resulting heterogeneous mixture was stirred vigorously at 30 °C, until GC analysis indicated complete consumption of the reactants.

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Notes

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† Electronic Supplementary Information (ESI) available: Experimental details, characterization data, and copies of NMR spectra of all compounds. See DOI: 10.1039/b000000x/

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