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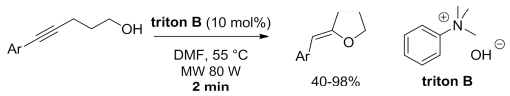

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Catalytic and metal-free intramolecular hydroalkoxylation of alkynes.

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ABSTRACT

Benzyltrimethylammonium hydroxide act as an efficient metal-free catalyst for the intramolecular hydroalkoxylation of alkynes. Notably, the use of microwave irradiation allowed reaction to operate in only two minutes. Under optimized reaction conditions, linear alkynes bearing aryl and heteroaryl substituents were successfully cyclized with good level of stereoselectivity.

Introduction

Exocyclic enol ethers are a class of heterocycle present in a range of natural or pharmacology active molecules [1]. (Figure 1). Moreover, they are useful intermediates for the synthesis of important biomolecules subunits such as C-glycosides [2a,b] or spirodiketal [2c].

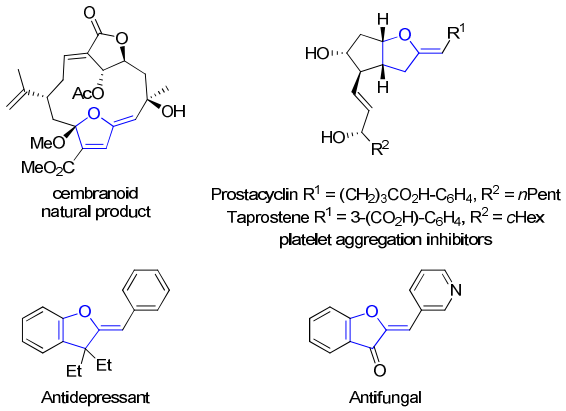


Figure 1. Naturally occurring and biologically active exocyclic enol ethers.

Early strategies for their synthesis relied on the olefination of parent lactones or isomerisation of endocyclic enol ethers [3]. Intramolecular hydroalkoxylations of alkynes represent a straight and atom-economical alternative to construct such oxygenated heterocycles, that could be promoted by numerous metals. Due to their toxicity, mercury salts [4] have been replaced with transition metals such as palladium [5a–d], platinum [5e], indium [5f], copper [5g,h], silver [5i], gold [6] or even lanthanide and actinide complexes [7]. In sharp contrast, base mediated cyclisation are much more difficult in absence of any electrophilic activation of the alkyne moiety and consequently less investigated. With exception of one reaction reported by Knochel [8a], only conformationally favourable cyclizations leading to benzofurans and involving excess of inorganic bases are documented (Figure 2) [8b-e].

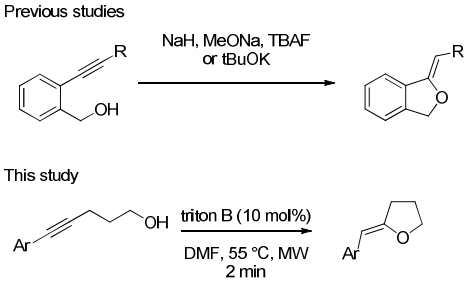


Figure 2. Context of base mediated hydroalkoxylation of alkynes.

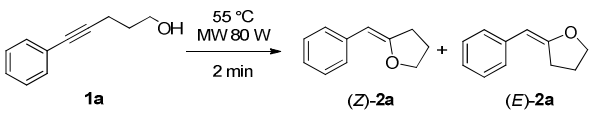
In the context of our recent study regarding selective pyrrolidine and pyrrole synthesis [9] we recently discovered that linear alkynes substituted with an appropriate alcohol moiety could be rapidly cyclized through a specific combination of a small amount of Triton B (benzyltrimethylammonium hydroxide) and microwave irradiations. The overall process conveniently

yielded the corresponding 5-membered exocyclic enol ethers in a catalytic and metal-free manner.

Results and discussion

Our investigations started with the attempted cyclization of inactivated alcohol **1a** under moderate microwave irradiations. Using catalytic amount of cesium or potassium hydroxide as base in highly polar solvents such as *N*-methylpyrrolidone (NMP) or dimethylsulfoxyde (DMSO), no conversion to the desired cyclic enol ethers **2a** was observed (Table 1, Entry 1 and 2). Switching to tetrabutylammonium fluoride in dimethylformamide (DMF) did not promote the reaction. Surprisingly, when using the strong organic bases tetrabutyl ammonium hydroxide (TBAH), a clean 5-*exo*-dig cyclisation of alcohol **1a** was observed in very short reaction time and expected selectivity favouring isomer (*Z*)-**2a**.[8b] Moreover, Triton B gave a slightly improved selectivity with a (*Z*)-**2a**:(*E*)-**2a** ratio of 88:12 (Table 1, Entry 6). Thus, non-activated alkyne **1a** was efficiently cyclized upon *a catalytic and metal-free process*.

Table 1
Optimization of **1a** 5-*exo*-dig cyclization.



Entry	Conditions	Yield (%) (Z):(*E*)-**2a**[a]
1	CsOH (20 mol%), DMF	0
2	KOH (20 mol%), DMSO/$H_2$0 15:1	0
3	KOH (20 mol%), DMSO	0
4	TBAF (10 mol%), DMF	0
5	TBAH (10 mol%), DMF	>95 (85:15)
6	Triton B (10 mol%), DMF	>95 (88:12)
7	Triton B (5 mol%), DMF	>95 (88:12)
8	Triton B (1 mol%), DMF	0
9	Triton B (10 mol%), 1,4-dioxane[b]	0
10	Triton B (10 mol%), toluene[b]	0
11	Triton B (10 mol%), THF[b]	0
11	Triton B (10 mol%), CH_3CN[b]	>95 (65/35)
12	Triton B (10 mol%), DMSO[b]	>85 (88/12)

[a] Isolated as a (*Z*/*E*) mixture, yield and ratio determined by ^{1}H NMR. [b] 60 °C, 3,5 min.

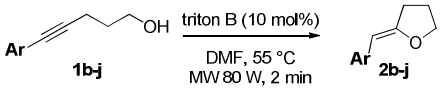
The amount of Triton B could be decreased to 5 mol% (Table 1, Entry 7). When 1 mol% Triton B was used, no conversion was observed after 2 minutes. Increased concentration gave a complex mixture of unidentified products while decreasing the temperature at 40 °C led to reproducibility problems.

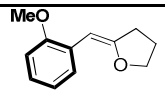
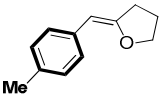
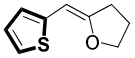
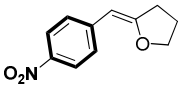
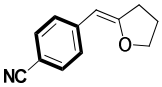
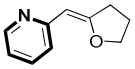
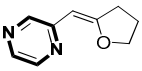
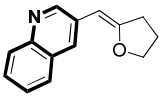
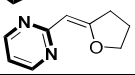
The nature of the solvent has a decisive influence on the result of the reaction: dioxane, toluene or THF gave no conversion, in line with known ineffective microwave heating in solvents with low dielectric constant [10]. More polar solvent such as acetonitrile gave complete conversion with a lower (*Z*)-**2a** selectivity and dimethyl sulfoxide (DMSO) provided similar selectivity as DMF, although inseparable side products (< 10%) were detected in the crude reaction mixture (Table 1, Entries 11 and 12).

To assess the critical effect of microwave irradiations, control experiments with one equivalent of Triton B at room temperature or at 100 °C using a conventional oil bath heating were performed. After a prolonged period (3-12 hours), no conversion was observed. However, increasing the temperature to 120 °C during 10 hours finally gave a lower 84% conversion and no selectivity (*Z*/*E* 55:45).

With optimized conditions in hand, the scope of the catalytic reaction was explored with various alcohols (Table 2).

Table 2
Scope of Triton B-mediated cyclization of arylalkynyl alcohols.



Entry			Yield %)[a]	(Z):(*E*)[a]
1		**2b**	81	88:12
2		**2c**	40	87:13
3		**2d**	44	75:25
4		**2e**	> 98	93:7
5		**2f**	> 98	87:13
6		**2g**	88	60:40, 98:2[b]
7		**2h**	86	63:37, 98:2[b]
8		**2i**	87	88:12, 98:2[b]
9		**2j**	90	96:4

Isolated yields; Z/E ratio determined by ^{1}H NMR of crude mixture;
[a] Over 2 steps after hydrogenation using Pd/C, see SI for details;
[b] After treatment with CF_3CO_2H, see SI for details.

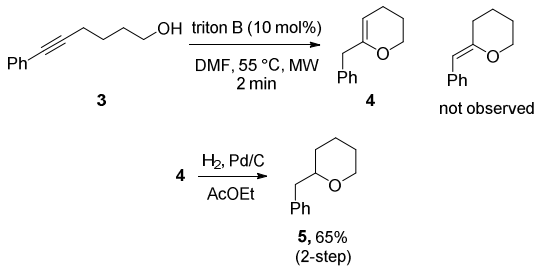
Thus electron-rich arenes connected to alkynyl alcohols were successfully reacted and converted into cycloethers **2b**-**2d** with moderate (*Z*)-selectivity. Those heterocycles displayed poor stability and required an additional reduction step (Pd/C, AcOEt, H_2) to be isolated, providing 2-substituted tetrahydrofurans in 81-40% yield over 2 steps.

Having a lower LUMO, electron-poor alkynes gave better results leading to stable cyclic ethers **2e** and **2f** in excellent yields (> 98%). Furthermore, pyridine, pyrazine, quinoline and

pyrimidine substituted alkynes were similarly cyclized in **2h–j** with excellent yields (86–90%). In some instances, moderate stereoselectivities were enhanced by isomerisation upon work-up with trifluoroacetic acid in dichloromethane (**2h–i**). This was rationalized in terms of increased stabilization of (*Z*)-**2g–i** through intramolecular hydrogen bonding between the oxygen atom and the protonated heterocycle. The substitution of the alkyne with electron depleted heterocycles facilitated considerably the cyclization process. Hence, a control experiment showed that **1g** (Ar = 2-pyridyl) cyclized into **2g** in 93% yield (*Z*/*E* 66:34) at room temperature, but at a much slower pace over 5 hours. Replacing the ammonium hydroxide with catalytic 1,8-diazabicyclo-[5.4.0]undec-7-ene or 1,1,3,3-tetramethylguanidine failed to promote the cyclization of **1g** at room temperature.

The possibility to obtain cyclic enol ethers substituted with Lewis basic nitrogen heterocycles further illustrate the versatility of this metal-free process. However, some limitations were noted: no cyclization occurred with 4-pentyn-1-ol and trimethylsilyl-substituted alkyne led only to clean desilylation. With more robust triisopropylsilyl group, only degradation compounds were observed.

Intramolecular hydroalkoxylation of alkyne leading to a 6-membered heterocycle is considerably less documented than 5-membered counterpart. Therefore cyclization of homologous phenylhexynol **3** was attempted. Upon treatment with Triton B, a 6-*exo*-dig cyclization took place followed by an isomerization, providing dihydropyran **4** with >90% NMR purity (Scheme 2) [11].



Scheme 2. 6-*exo*-*dig* cycloisomerization of phenylhexynol **3**

Poor stability of compound **4** prevented further purification by flash chromatography and subsequent hydrogenation afforded tetrahydropyran **5** in 65% yield over 2 steps.

Conclusion

In summary, we have developed 5-exo-dig cyclizations of arylalkynyl alcohols under unprecedented tetraalkylammonium hydroxide catalysis. One example of 6-exo-dig cyclization is also reported. Without favorable bias such as present in benzylic alcohol derived alkynes, the chemistry is compatible with alkynyl connected to electron-rich or electron-poor aryl groups with similar efficiency. In all cases, good to excellent stereoselectivities in favour of the (*Z*)-enol ethers were obtained. The base used in this reaction, Triton B, is readily available, easy to handle and was used in catalytic amount. Further studies to clarify the reaction mechanism, in particular the contribution of the counter cation are currently in progress in our laboratory.

Acknowledgments

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