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Synthesis of [3.3.1] Bicyclic Compounds by a Brønsted Acid Catalysed Double Intramolecular Michael Addition

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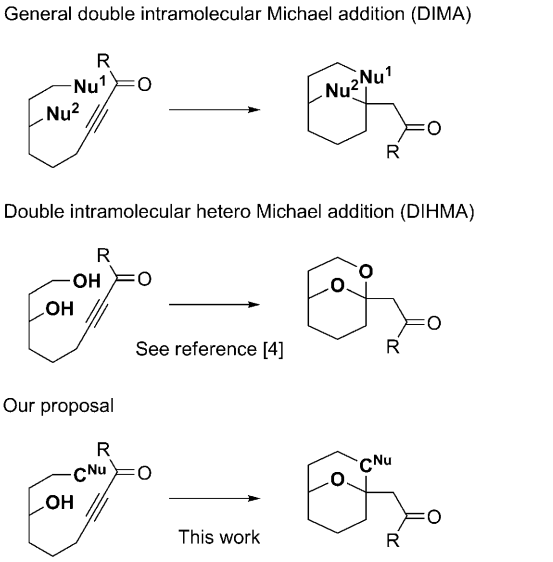
Dedicated to Professor José Barluenga on the occasion of his 70th birthday

One of the current challenges in organic chemistry is the development of tandem reactions (domino or cascade reactions) that provide complex molecules from readily available starting compounds.[1] A major subject of research in this field is the exploration of new tandem reactions promoted by a single catalyst.[2] In particular, some elegant organocatalytic cascade reactions promoted by both chiral amines or Brønsted acids have been developed.[3]

The double intramolecular hetero Michael addition (DIHMA) of a diol upon an ynone is an effective approach to give several ketal derivatives.[4] In these reactions, two hydroxyl groups act as the nucleophilic counterpart that adds to the β carbon of the alkyne of the ynone (Scheme 1b). These DIHMA reactions may be considered as a particular case of the double intramolecular Michael addition (DIMA) in which two general nucleophiles add to an ynone (Scheme 1a). However, as far as we know, this interesting DIMA reaction has not been expanded further than those particular cases in which both nucleophiles are hydroxyl groups (DIHMA). In this context we were attracted by the work developed by C. J. Forsyth et al., about the use of the DIHMA reaction for the synthesis of 2,9-dioxabicyclo-[3.3.1]nonane derivatives.[4a] We thought that simple 9-oxabicyclo[3.3.1]nonane derivatives could be obtained by an unexplored double intramolecular Michael addition of an oxygen-centred and a carbon-centred nucleophile to an ynone (Scheme 1c).

Note that we had previously evaluated another approach to access these types of bicyclic compounds. Thus, by using carbophilic Lewis acids (π acids) we were able to activate simple alkynes that favour a double addition of two different nucleophiles to a non-functionalised C≡C triple bond.[5] One of the main drawbacks of this strategy is the necessity of using precious organo–transition-metal catalysts as promoters of the reaction. We thought that we could surpass this problem by applying the DIMA strategy above because, in principle, the metallic catalyst could be substituted by cheaper and easily handled Brønsted acids. Also note that the mode of activation of Brønsted acids is different from that of the π acids because these activate the alkyne and the Brønsted acids activate the carbonyl group that favours the double Michael addition.

Herein we wish to detail the first examples of double intramolecular Michael addition of two different nucleophiles



Scheme 1. Concept of the double intramolecular Michael addition (DIMA), previous DIHMA strategies and our proposal.

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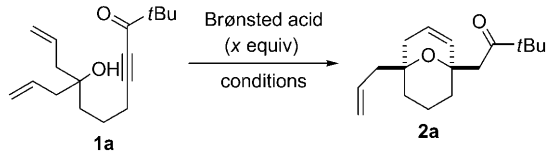
(an oxygen-centred and a carbon-centred nucleophile) to an ynone. This novel Brønsted acid catalysed reaction allows the synthesis of 9-oxabicyclo[3.3.1]nonane derivatives in a straightforward manner.

Initial attempts to promote the double intramolecular Michael addition (DIMA) were performed with the model diallyl-substituted ynone derivative **1a** as a starting material. With the previous work in the field that was commented on above in mind,[4] we were confident about the ability of the hydroxyl group to act as an oxygen-centred nucleophile. Our concerns were about the capacity of the alkene to act as a carbon-centred nucleophile in a Michael-type addition reaction. Gratifyingly, ynone **1a** reacted in dichloromethane in the presence of one equivalent of triflic acid (CF_3SO_3H) to give the desired 9-oxabicyclo[3.3.1]nonane derivative **2a** in a pleasing 88% yield as a single regio- and diastereoisomer (Table 1, entry 1). At this time we were pleasantly surprised by the formation of a single regio- and diastereoisomer of the final product, because in our early work with simple alkynes and metal catalysts we had observed the formation of equimolecular mixtures of two regioisomeric endocyclic alkenes.[5c] It seems that the presence of the carbonyl group directly attached to the triple bond has a positive effect that favours in some way the formation of a single regiosomer. This initial experiment led us to evaluate other catalysts and/or reaction conditions (Table 1).

Table 1. Cycloisomerisation reactions of the alkynol **1a**—optimisation of the catalyst.



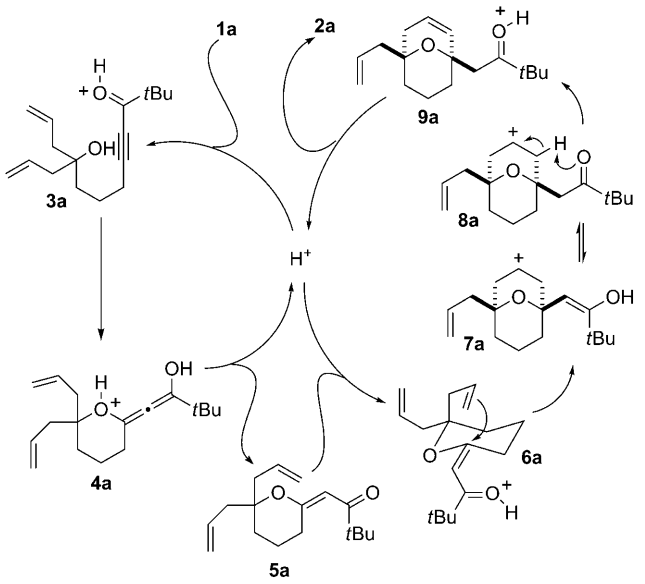
1a **2a**

Entry	Brønsted acid	No. of equiv	Conditions[a]	Yield [%][b]
1	CF_3SO_3H	1	CH_2Cl_2, 0°C to RT, 2 h	88
2	$HBF_4{\cdot}OEt_2$	1	CH_2Cl_2, 0°C to RT, 2 h	92
3	CF_3SO_3H	0.5	CH_2Cl_2, 0°C to RT, 16 h	86
4	CF_3SO_3H	0.25	CH_2Cl_2, 0°C to RT, 48 h	84
5	PS–PTSA[c]	1	$ClCH_2CH_2Cl$, 70°C, 24 h	92
6	PS–PTSA[c]	1	dioxane, 130°C, MW, 10 min	98[d]
7	PS–PTSA[c]	0.5	dioxane, 130°C, MW, 10 min	70[e]
8	PS–PTSA[c]	0.5	dioxane, 130°C, MW, 45 min	88[e]

[a] Unless otherwise stated the time shown is that required to reach >99% conversion. [b] Isolated yield of spectroscopically pure product **2a**. [c] PS–PTSA: Polymer-bound *p*-toluenesulfonic acid. [d] The recovered PS–PTSA was reused in a new reaction, and under similar reaction conditions 96% of **2a** was isolated. [e] Refers to the conversion estimated by ^1H NMR spectroscopy of the crude of the reaction. The remaining compound corresponds to the oxy-Michael product.

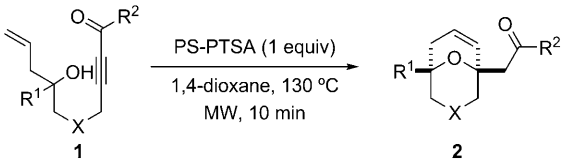
Apart from triflic acid, other Brønsted acids such as tetrafluoroboric acid (1 equivalent) were proven to be effective catalysts to perform the desired reaction (Table 1, entry 2). As shown, to achieve complete conversion of the starting material in a relative short time, one equivalent of the corresponding Brønsted acid was used. However, we observed that the reaction could also be performed under truly catalytic conditions. So, by lowering the catalyst loading to 0.5 equivalents of triflic acid, 16 h were required for the complete conversion of the starting material (Table 1, entry 3). Finally, the use of only 0.25 equivalents of triflic acid resulted in a significant increase of the reaction time required for complete conversion of the starting material (Table 1, entry 4). It is remarkable that this model reaction could also be performed by using commercially available polymer-bound *p*-toluenesulfonic acid (PS–PTSA). Similar or even slightly higher yields were obtained under these conditions and, moreover, the isolation of the product by simple filtration of the solid supported acid was much easier (Table 1, entry 5). The only limitation we found when using PS–PTSA as a promoter of the reaction was the relatively long time required for complete conversion of the starting alkynol **1a**. Microwave heating has emerged as a versatile method to speed up many chemical processes, so we decided to try our reaction under microwave irradiation. Thus, under optimised conditions complete cyclisation of **1a** took place in just 10 min at 130°C in dioxane as solvent affording compound **2a** in 98% yield (Table 1, entry 6). Note that the recovered PS–PTSA maintained its catalytic activity as demonstrated by an experiment performed with the filtered PS–PTSA in which we observed essentially the same yield of **2a** as with fresh PS–PTSA (Table 1, entry 6). As before, we observed that lowering the amount of PS–PTSA results in an increasing of the reaction time (Table 1, entries 7 and 8).

A tentative mechanism for the formation of 9-oxabicyclo-[3.3.1]nonane derivative **2a** is presented in Scheme 2. Initial interaction of the proton of the Brønsted acid with the oxygen of the carbonyl group of **1a** gives rise to intermediate **3a**. This interaction would favour the intramolecular conjugated addition of the hydroxyl group to deliver **4a**. The release of a proton followed by a keto–enol tautomery would lead to the formation of the β-alkoxyenone derivative **5a** regenerating the acid catalyst in a formal oxy-Michael-type cyclisation process. The second catalytic cycle would imply again an initial interaction of the proton of the Brønsted acid with the oxygen of the carbonyl group of **5a** to form intermediate **6a**. Further conjugated addition of the double bond of one of the allyl groups to this activated intermediate **6a** would result in the formation of cationic intermediate **7a**. This cyclisation step is believed to proceed through a chair-like transition state in which only the axial allyl moiety reacts. This rationalisation is consistent with the configuration of the stereogenic centers observed in **2a**. From **7a** we suppose a keto–enol tautomery leading to **8a**. Finally, an elimination of a proton would explain the formation of the final product **2a** through intermediate **9a**. As previously stated, in contrast to our previous results with related alkynol derivatives lacking the carbonyl group at the triple bond,[5c] we observed the formation of a single regioisomer of **2a**. So, we suppose that the final elimination reac-



Scheme 2. Proposed mechanism for the formation of eight-membered compound **2a** from ynone **1a**.

Table 2. Reaction of the ynone derivatives **1** to give bicyclo[3.3.1]nonane derivatives **2**.



Alkynol	R^1	R^2	X	product	yield [%][a]
1a	allyl	*t*Bu	CH_2	**2a**	98
1b	allyl	cyclohexyl	CH_2	**2b**	92
1c	allyl	Me	CH_2	**2c**	90
1d	$Ph(CH_2)_2$	*t*Bu	CH_2	**2d**	95
1e	allyl	4-ClC_6H_4	CH_2	**2e**	92
1f	H	4-FC_6H_4	CH_2	**2f**	90[b]
1g	allyl	2,4-$Cl_2C_6H_3$	O	**2g**	94[c]
1h	allyl	cyclohexyl	O	**2h**	97

[a] Isolated yield of spectroscopically pure product **2**. [b] 6.3:1 mixture of regioisomers. [c] 10.5:1 mixture of regioisomers.

tion is selective owing to the presence of the carbonyl group in **1a**. In fact, we believe that in intermediate **8a** the oxygen of the carbonyl group may act as a base by taking one of the spatially close protons (through a six-membered transition state) to give the observed regioisomer **2a**.

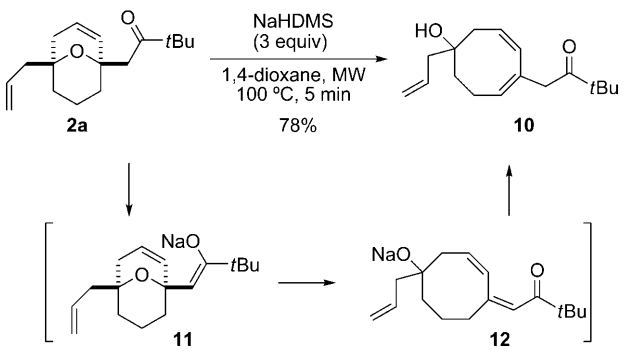
Once we had found the appropriate catalysts and conditions to perform the reaction, we focused on the scope of this process. Having established that the microwave irradiation conditions were appropriate to obtain the final product in high yield and short time, we decided to use these conditions for the generalisation of the reaction. Moreover, we used the polymer-supported PS–PTSA as the catalyst of the reaction owing to the easiness of purification of the final product (a simple filtration and removal of solvent) and the possibility of reusing it.

As shown in Table 2, different substituents on both the carbon containing the hydroxyl group and the ketone moiety were tolerated. Also, a number of experiments were attempted by using ynone derivatives **1** as starting materials, which contain a heteroatom in the chain that connects the hydroxyl functionality and the triple bond. As shown, all reactions led to the expected bicyclic compounds in high yield. Note that in most cases only one regio- and diastereoisomer of the final product was formed. In fact, we only observed the presence of a minor regioisomer with ynone derivatives **1f** and **1g**.

The rich reactivity of the carbonyl group could be a good opportunity to obtain functionalised products from bicyclo-[3.3.1]nonane derivatives **2**. In this context, we thought that it could be possible and interesting to transform compounds **2** into eight-membered carbocycles through a retro-oxy-Michael reaction by treatment with a base. Note that the development of new approaches to eight-membered carbocycles continues to be an important synthetic challenge owing to the well-known difficulties associated with the construction of these medium-sized cyclic structures.[6]

To check the feasibility of the proposed retro-oxy-Michael reaction for the synthesis of eight-membered carbocycles, we selected compound **2a** as a model substrate. After some optimisation of the reaction conditions we observed that the best base was sodium bis(trimethylsilyl)amide (NaHDMS) and that again, the microwave irradiation had a positive effect both on the yield and the speed of the reaction. Thus, treatment of 9-oxa-bicyclo[3.3.1]nonane derivative **2a** with 3 equivalents of NaHDMS in 1,4-dioxane as the solvent at 100 °C under microwave irradiation led to the formation of cyclooctadiene derivative **10** in 78% yield in just 5 min (Scheme 3).

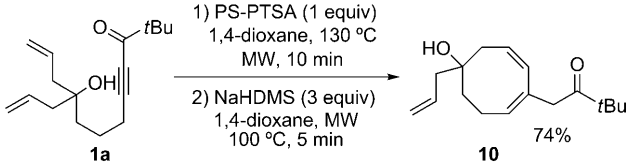
This reaction is supposed to proceed through an initial deprotonation of ketone derivative **2a** to give the enolate **11**. Subsequent retro-oxy-Michael reaction delivers the eight-membered carbocycle **12**. This intermediate finally evolves by an isomerisation of the exocyclic double bond to an en-



Scheme 3. Synthesis of eight-membered carbocycle **10** from compound **2a** through a retro-oxy-Michael reaction.

docyclic position furnishing the final product **10** after hydrolysis.

As shown, we found that both reactions, the double intramolecular Michael Addition and the retro-oxy-Michael reaction may be performed under the same reaction conditions (microwave irradiation and the same solvent). So, we developed a straightforward procedure for the transformation of ynone derivative **1a** into the eight-membered carbocycle **10** through a consecutive reaction (Scheme 4). Thus,

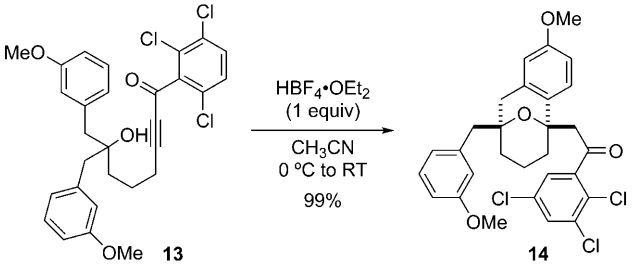


Scheme 4. Synthesis of cyclooctanol derivative **10** from ynone **1a** through a consecutive reaction.

we reacted compound **1a** in the presence of PS–PTSA at 130 °C in dioxane under microwave irradiation for 10 min. Then, NaHDMS was added to the mixture and heated, again, under microwave irradiation at 100 °C for 5 min. As shown, this process does not require any change of solvent or the isolation of intermediates. The only operation required is a simple filtration step and the final product may be obtained after just 15 min. Note that this easy procedure for the synthesis of eight-membered carbocycle derivatives from ynones appears to be amenable for continuous-flow microreactor chemistry.[7]

To know whether a different carbon-centred nucleophile could participate in our proposed double intramolecular Michael addition, we performed a final experiment with ynone derivative **13** that contains an aryl group instead an alkene (Scheme 5). We were pleased to find that this reaction led to the expected benzofused bicyclo[3.3.1]nonane derivatives **14** in practically quantitative yield and as single diastereoisomer.[8]

In conclusion, we have developed a new, highly efficient method for the synthesis of complex [3.3.1] bicyclic compounds from easily available ynone derivatives. The reaction is based on a double intramolecular Michael addition (DIMA) catalysed by Brønsted acids. To the best of our knowledge, this is the first general reaction of this type in which two nucleophiles of different nature are used. In particular, we have investigated the DIMA reaction in which an oxygen-centred and a carbon-centred nucleophile add to an ynone derivative. Also remarkable is the possibility of performing these reactions under microwave irradiation and by using polymer-supported protic acids. This allows the final products to be obtained in short times after a simple filtration, which indicates at the same time that our method could be of interest in the emerging field of continuous-flow microreactor chemistry. Moreover, the [3.3.1]bicyclic systems obtained through this strategy are natural-like structural motifs that might be of value in the discovery of biologically active molecular agents.



Scheme 5. Benzofused bicyclo[3.3.1]nonane **14** by DIMA reaction of ynone derivative **13**.

Acknowledgements

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Keywords: bicycles · Brønsted acids · cyclization · Michael addition · ynones

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[8] Preliminary experiments show that this reaction proceeds more efficiently in acetonitrile as the solvent. The use of a lower amount of the catalyst only results in an increase in the time required for the consumption of the starting material. Other catalysts such as TMSOTf or PS–PTSA also promote the reaction. Full details will be given in a Full Paper.

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