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Synthesis of 2-phosphonoheterocycles *via* base-promoted 5-*endo* cyclization

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ABSTRACT

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Herein, a synthesis of 2-phosphonodihydrofurans and 2-phosphonodihydropyrroles *via* 5-*endo* cyclization of O- and N-propargylated compounds is described. The reaction is promoted by potassium *tert*-butoxide and allows a fast access to interesting heterocycles which were easily converted into 2-arylated pyrroles under acidic conditions.

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Introduction

Heterocyclic phosphonates have attracted considerable attention for many years, especially due to their remarkable activities.^[1] For instance, phosphonopyrrolidine **1** (Fig. 1) is known to exhibit bactericidal, fungicidal and herbicidal activities whereas phosphonotetrahydrofuran **2** has shown important HCMV and antitumor activities.^[2] In addition, the phosphonate group can mimic the carboxylic moiety found in some biologically active sugars such as the sialic acids.^[3] On the other hand, heterocyclic phosphonates could be important synthetic intermediates as shown by isoindolinone **3** which may be used for the synthesis of important biologically active alkaloids (Fig. 1).^[4]

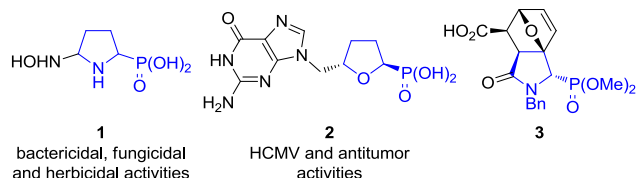
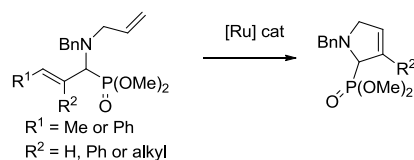


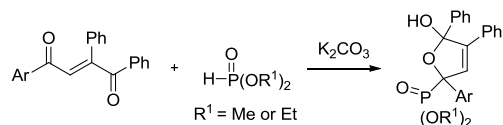
Figure 1. Selected valuable 2-phosphonoheterocycles

For all these reasons, several research groups turned their attention to the development of new synthesis of heterocyclic phosphonates. Concerning dihydropyrroles and dihydrofurans, several approaches were developed.^[5] Ring-closure metathesis, which is a classical method to obtain this kind of heterocycles,^[6] was applied to the synthesis of 2-phosphono-2,5-dihydropyrroles (Scheme 1.a) as well as dihydrofurans.^[7] Except this ruthenium-catalyzed transformation, only few methods were developed for the synthesis of 2-phosphonodihydropyrroles or dihydrofurans. Recently, the group of Touil developed a base-promoted reaction between 1,4-diones and dialkyl phosphites to obtain 2-phosphono-2,5-dihydrofurans (Scheme 1.b).^[8] Another method to obtain phosphonodihydropyrroles was based on a metal-catalyzed cycloisomerization of (hydroxy)allenes (Scheme 1.c).^[9] By examining the literature examples, no easy and general method has been reported. The starting material synthesis often required several steps whereas the scope of the reaction is relatively limited. Concerning the formation of dihydrofurans or dihydropyrroles, we and other groups have explored the potential of alkyne in various 5-*endo-dig* cyclization strategies.^[10] Indeed, in 2012, the group of Miranda first reported a synthesis of 2,3-dihydropyrroles from N-propargyl Ugi adducts whereas we recently developed a 2,5-dihydrofuran synthesis *via* a 5-*endo-dig* cyclization of O-propargyl mandelic acid amides induced by potassium *tert*-butoxide (Scheme 1.d). Based on these results, we were keen to develop a 5-*endo-dig* cyclization reaction to get a direct access to 2-phosphonodihydropyrroles and 2-phosphonodihydrofurans (Scheme 1.e).

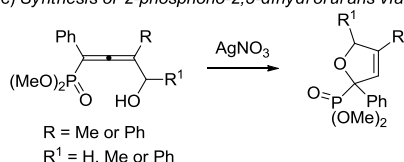
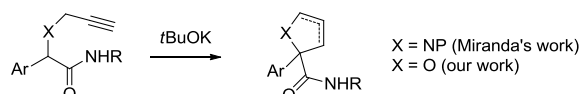
a) Synthesis of 2-phosphono-2,5-dihydropyrroles via RCM:



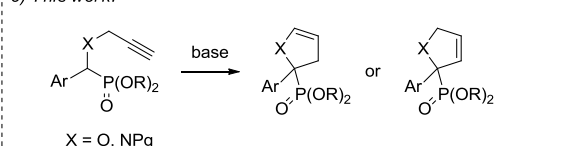
b) Base-promoted synthesis of 2-phosphono-2,5-dihydrofurans



c) Synthesis of 2-phosphono-2,5-dihydrofurans via cycloisomerization

d) Previous works on 5-*endo-dig* cyclization:

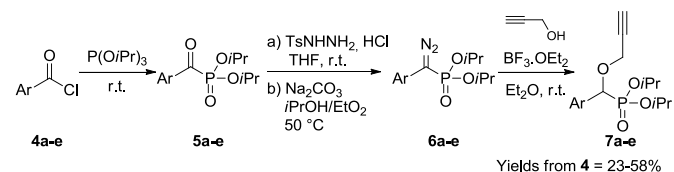
e) This work:



Scheme 1. Synthesis of 2-phosphonodihydropyrroles and dihydrofurans

Results and discussion

At the outset, we focused our attention on the synthesis of 2-phosphonodihydrofurans. For that, several O-propargylated starting materials **7a-e** were synthesized through an alcohol insertion into diazo group strategy (Scheme 2).^[11] Starting from acyl chlorides **4a-e**, different α -keto phosphonates **5a-e** were obtained and directly transformed into corresponding diazo phosphonates **6a-e**. Finally, an acid-catalyzed insertion of propargylic alcohol delivered expected O-propargylated starting materials **7a-e** in good overall yields.^[12]

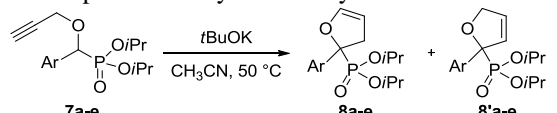


Scheme 2. Synthesis of O-propargylated starting materials

Then, based on our former results on 5-*endo-dig* cyclization,^[10c] phosphonoalkynes **7** were treated with 1.5 equivalent of potassium *tert*-butoxide in acetonitrile (Table 1). Reactions were carried out on diisopropyl phosphonate compounds which are more tolerant of basic conditions than less hindered phosphonates. When alkyne **7a**, with a *para*-methylbenzene substituent, was submitted to the conditions, a mixture of 2,3-dihydrofuran **8a** (49% yield) and 2,5-dihydrofuran **8'a** (8% yield) was obtained (Table 1, entry 1). Different *para* substituted compounds were tested under the reaction conditions and, when the aromatic moiety was functionalized with a fluorine or a methoxy group, 2,3-dihydrofurans **8b** (50% yield) and **8c** (57% yield) were

isolated as the only product (Table 1, entry 2 and 3). However, alkyne **7d** with a phenyl group in *para* position delivered a mixture of regioisomers in favor of 2,5-dihydrofuran **8'd** (Table 1, entry 4). Finally, *meta*-methylsubstituted 2,3-dihydrofuran **8e** was synthesized despite a slightly lower yield (Table 1, entry 5, 36% yield).

Table 1. Scope of the dihydrofuran synthesis^[a]

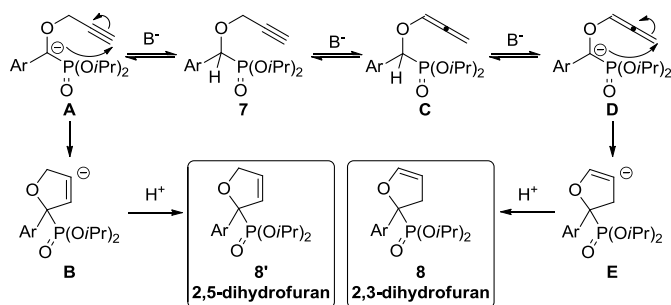


Entry	Ar	8a-e ^[b]	8'a-e ^[b]
1		49%	8%
2		50%	-
3		57%	-
4		15%	45%
5		36%	-

^a Reactions were carried out with substrate **7** (0.5 mmol) and *t*BuOK (1.5 mmol, 1.5 eq.) in CH₃CN (2 mL).

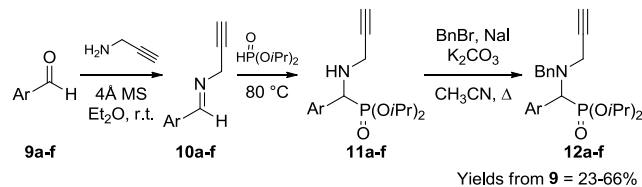
^b Isolated yields.

In order to explain the formation of the two observed dihydrofuran regioisomers, two possible pathways are proposed in scheme 3. 2,5-Dihydrofuran **8'** may result on the direct attack of the deprotonated form of **7** onto the alkyne moiety. Indeed, after deprotonation, **A** may cyclize in a 5-*endo-dig* fashion to form anion **B** which, after reprotonation, delivers the 2,5-dihydrofuran scaffold. However, the alkyne moiety may first isomerize into allene **C** which would be then deprotonated. A 5-*endo-trig* cyclization of **D**, followed by reprotonation, would explain the formation of 2,3-dihydrofuran **8**.



Scheme 3. Involved mechanism for the synthesis of the two regioisomers

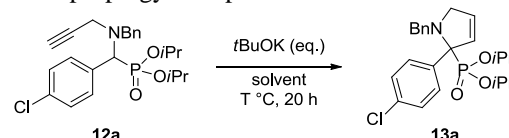
After having synthesized 2-phosphonodihydrofurans, we were keen to extend the reaction to nitrogenated substrates. In this objective in mind, N-propargylated imines **11a-f** were synthesized from several aldehydes **9a-f** via a Kabachnik-Fields reaction (scheme 4). After a benzyl protection, desired nitrogenated starting materials **12a-f** were obtained in good overall yields.



Scheme 4. Synthesis of N-propargylated starting materials

For the cyclization, the former conditions were applied to propargyl **12a** but 2,5-dihydropyrrole **13a** was isolated in a poor 9% yield (Table 2, entry 1). Moreover, a significant amount of depropargylation of starting material **12a** was observed during the reaction. Taking into account literature precedents,^[10a] THF was used as solvent and, with 2.5 equivalents of potassium *tert*-butoxide, a 12% yield of **13a** was observed at room temperature (Table 2, entry 3) and a 32% yield was obtained at 50 °C whereas no depropargylation was observed at this temperature (Table 2, entry 4). Finally, more polar solvents were tested and dihydropyrrole **13a** was isolated in 42% yield when DMSO was used as solvent (Table 2, entry 6).

Table 2. Optimization of the 5-*endo-dig* cyclization on the nitrogenated propargyl compound^[a]



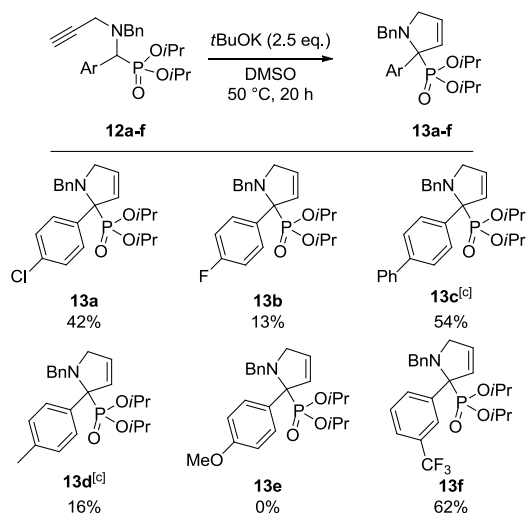
Entry	<i>t</i> BuOK (eq.)	solvent	T (°C)	Yield ^[b] (%)
1	1.5	CH ₃ CN	50	9 ^[c]
2	1.5	THF	r.t.	0
3	2.5	THF	r.t.	12 ^[c]
4	2.5	THF	50	32
5	2.5	DMF	50	28
6	2.5	DMSO	50	42

^a Reactions were carried out with substrate **12a** (0.5 mmol) in 2 mL of solvent.

^b Isolated yields.

^c Formation of a depropargylated side-product.

We next investigated the scope of the reaction using these new conditions (Scheme 5). Different propargyl **12** were engaged in the cyclization reaction and, in all cases, 2,5-dihydropyrroles **13** were obtained as only regioisomers. 2,5-Dihydropyrroles **13a** and **13b**, bearing a *para*-halogenated aromatic group, were isolated in moderate yields (42% and 13% respectively). Then, when the aromatic moiety was substituted with a phenyl or methyl group in *para* position, the cyclization reaction was carried out with DMF as solvent and desired dihydropyrroles **13c-d** were obtained in moderate to good yields (54% and 16% respectively). Contrary to dihydrofuran synthesis, no desired cyclized product was observed with a methoxy group in *para* position. Very interestingly, 2,5-dihydropyrrole **13f**, bearing a *meta*-substituted aromatic group, was isolated in a good 62% yield.



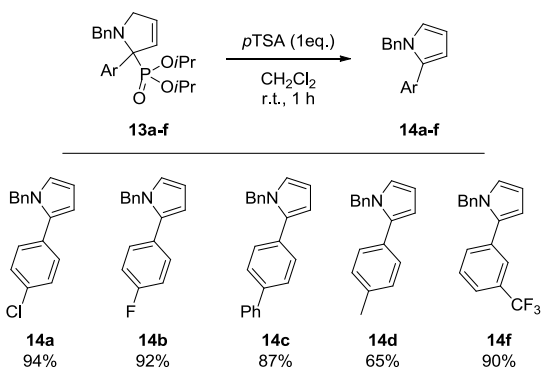
Scheme 5. Scope of the dihydropyrrole synthesis^[a,b]

^aReactions were run on 0.5 mmol scale.

^bIsolated yields.

^cDMF was used as solvent.

With this straightforward approach to dihydropyrroles in hand, we envisioned that the interest of the method could be raised by allowing reaching pyrroles from the same starting materials. Pyrrole is a very important heteroaromatic scaffold in chemistry due to its interesting properties in biology and material chemistry.^[13] Its aromatic nature together with the leaving group ability of the phosphonyl moiety were in strong support for this potential transformation. Indeed, under acidic conditions (1 equivalent of *p*TSA in dichloromethane) 2-phosphonodihydrofurans **13a-f** underwent phosphorus elimination at room temperature to deliver corresponding pyrroles **14a-f** in very good yields (Scheme 6, 65 to 94% yields).



Scheme 6. 2-arylated pyrrole synthesis^[a]

^aIsolated yields.

Conclusion

In summary, we have developed a short synthesis of 2-phosphonodihydrofurans and pyrroles *via* a base-promoted 5-*endo* cyclization. Despite moderate yields, this method offers an easy access to a wide range of phosphono heterocycles which, in the case of dihydrofurans, represent very important sugar analogues. In addition, the phosphonate group could be easily eliminated under acidic conditions to deliver 2-arylated pyrroles. Further explorations of 5-*endo-dig* cyclizations are currently in progress in our group.

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