Tetrahedron Letters 64 (2021) 152742

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Ameni Bousbia [a], Mohamed Lamine Benkhoud [a], Laurent El-Kaïm [b], Sébastien Prévost [b,*]

[a] Laboratory of Physico-chemistry of Microstructures and Microsystems, Preparatory Institute for Scientific and Technical Studies, University of Carthage, BP51, 2078 La Marsa, Tunisia
[b] Laboratoire de Synthèse Organique, CNRS, Ecole Polytechnique, ENSTA, UMR 7652, Institut Polytechnique de Paris, 91128 Palaiseau, France

ARTICLE INFO

Article history:
Received 7 October 2020
Revised 30 November 2020
Accepted 4 December 2020
Available online 29 December 2020

Keywords:
5-Endo cyclization
Dihydrofurans
Dihydropyrroles
Phopshonates
Alkynes

ABSTRACT

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.

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].

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).

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

* Corresponding author.
E-mail address: sebastien.prevost@ensta-paris.fr (S. Prévost).

https://doi.org/10.1016/j.tetlet.2020.152742
0040-4039/

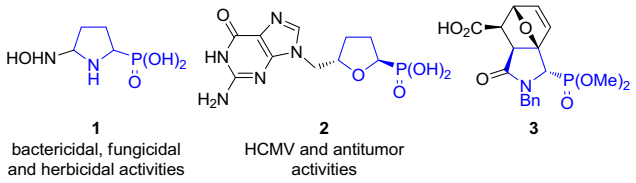
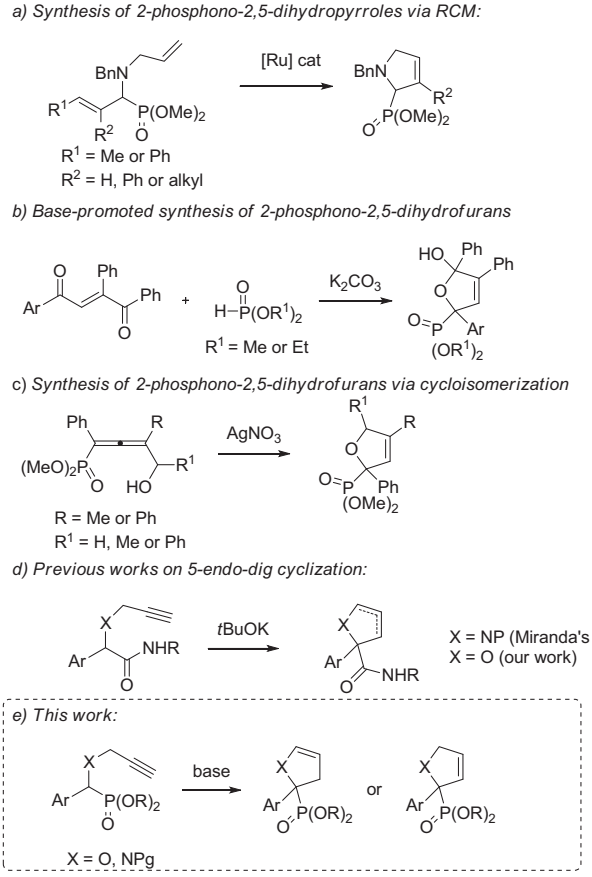
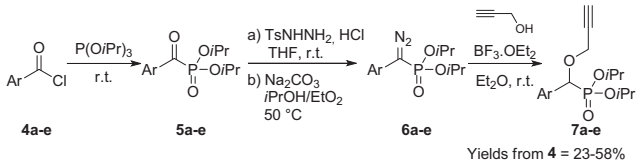


Fig. 1. Selected valuable 2-phosphonoheterocycles.



Scheme 1. Synthesis of 2-phosphonodihydropyrroles and dihydrofurans.

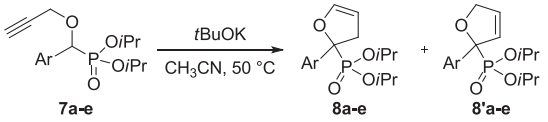


Scheme 2. Synthesis of O-propargylated starting materials.

expected O-propargylated starting materials **7a-e** in good overall yields [12].

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.

Table 1
Scope of the dihydrofuran synthesis.[a]



Entry	Ar (SM)	8a-e[b]	8′a-e[b]
1	Me- (7a)	49%	8%
2	F- (7b)	50%	–
3	MeO- (7c)	57%	–
4	Ph- (7d)	15%	45%
5	Me (7e)	36%	–

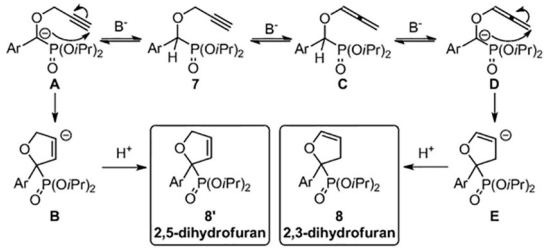
[a] Reactions were carried out with substrate **7** (0.5 mmol) and *t*BuOK (1.5 mmol, 1.5 eq.) in CH_3CN (2 mL).
[b] Isolated yields.

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).

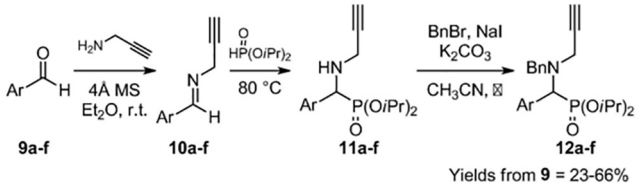
In order to explain the formation of the two observed dihydrofuran regioisomers, two possible pathways are proposed in scheme 3. 2,5-Dihydrofuran **8′** may result on the direct attack of the deprotonated form of **7** onto the alkyne moiety. Indeed, after deprotonation, **A** may cyclize in a 5-*endo-dig* 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**.

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.

For the cyclization, the former conditions were applied to propargyl **12a** but 2,5-dihydropyrrole **13a** was isolated in a poor



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



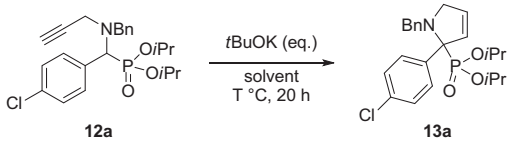
Scheme 4. Synthesis of *N*-propargylated starting materials.

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).

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 low to moderate 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.

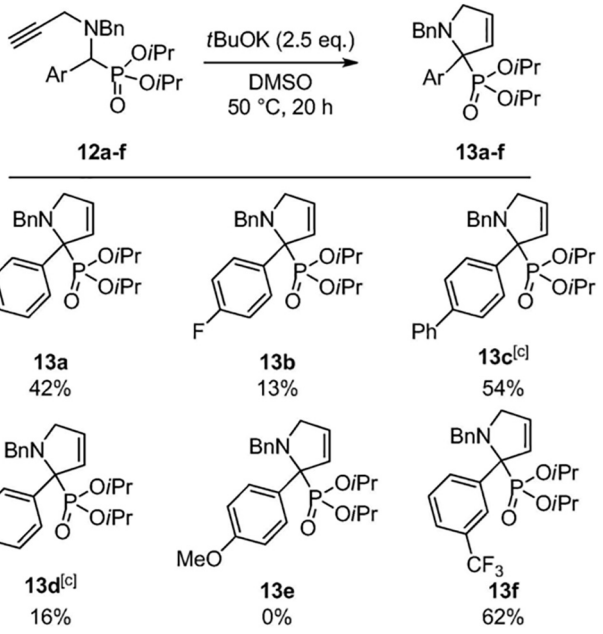
With this straightforward approach to dihydropyrroles in hand, we envisioned that the interest of the method could be raised by allowing reaching pyrroles from the same starting materials. Pyrrole is a very important heteroaromatic scaffold in chemistry due to its interesting properties in biology and 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-phosphonodihydropyrroles **13a-f** underwent phosphorus elimination at room temperature to deliver corresponding pyrroles **14a-f** in very good yields (Scheme 6, 65 to 94% yields).

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

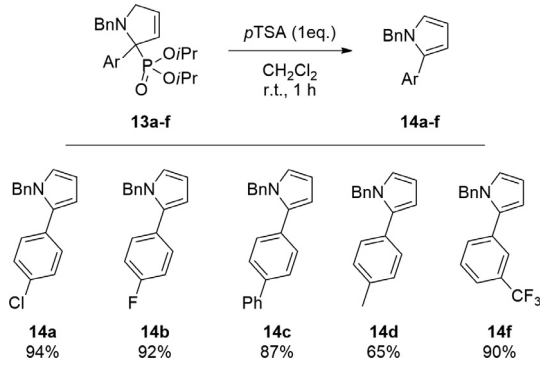


Entry	*t*BuOK (eq.)	solvent	T (°C)	Yield[b] (%)
1	1.5	CH_3CN	50	9[c]
2	1.5	THF	r.t.	0
3	2.5	THF	r.t.	12[c]
4	2.5	THF	50	32
5	2.5	DMF	50	28
6	2.5	DMSO	50	42

[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.



Scheme 5. Scope of the dihydropyrrole synthesis[a,b]. [a]Reactions were run on 0.5 mmol scale. [b]Isolated yields. [c]DMF was used as solvent.



Scheme 6. 2-Arylated pyrrole synthesis[a]. [a]Isolated 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.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Ms Vanessa Chen and Ms Farah Taieb-Tamacha are thanked for their assistance. The authors gratefully acknowledge the Ministry of Higher Education and Scientific Research of Tunisia (MHESR)

for the financial support through the Lab **LR11ES23**. The CNRS, ENSTA, Ecole Polytechnique and Institut Polytechnique de Paris are acknowledged for financial supports.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152742.

References

[1] (a) P.A. Gurevich, V.A. Yaroshevskaya, Chem. Heter. Comp. 36 (2000) 1361;
(b) K. Moonen, I. Laureyn, C.V. Stevens, Chem. Rev. 104 (2004) 6177;
(c) F. Orsini, G. Sello, M. Sisti, Curr. Med. Chem. 17 (2010) 264;
(d) L. Chen, X.-Y. Liu, Y.-X. Zou, Adv. Synth. Catal. 362 (2020) 1724.
[2] (a) Hassan, J. PCT Int. Appl., WO 2000004031, 2000; Chem. Abstr. 2000, 132, 108102.;
(b) P. Nguyen-Ba, N. Turcotte, L. Yuen, J. Bédard, M. Quimpère, L. Chan, Bioorg. Med. Chem. Lett. 8 (1998) 3561;
(c) J. Bédard, S. May, M. Lis, L. Tryphonas, J. Drach, J. Huffman, R. Sidwell, L. Chan, T. Bowlin, R. Rando, Antimicrob. Agents. Chemother. 43 (1999) 557;
(d) L. Leblond, G. Attardo, B. Hamelin, D.Y. Bouffard, N. Nguyen-Ba, H. Goudreau, Mol. Cancer Ther. 1 (2002) 737;
(e) M. Bubenik, R. Rej, N. Nguyen-Ba, G. Attardo, F. Oeullet, L. Chan, Bioorg. Med. Chem. Lett. 12 (2002) 3063.
[3] (a) J. Gao, V. Martichonok, G.M. Whitesides, J. Org. Chem. 61 (1996) 9538;
(b) T.-H. Chart, Y.-C. Xin, J. Org. Chem. 62 (1997) 3500.
[4] (a) G.O. Kachkovskyi, O.I. Kolodiazhnyi, Tetrahedron 63 (2007) 12576;
(b) E. Valencia, I. Weiss, S. Firdous, A.J. Freyer, M. Shamma, Tetrahedron 40 (1984) 3957;
(c) P.S. Sarang, A.A. Yavad, P.S. Patil, U.M. Krishna, G.K. Trivedi, M.M. Salunkhe, Synthesis (2007) 1091.
[5] (a) For reviews on dihydrofuran and dihydropyrrole synthesis, see: V.A. Slavinskaya, R.A. Karakhanov, L.Y. Brezhnev, I.I. Geiman, L.F. Bulenkova, A.K. Strautinya Chem. Heterocycl. Compd. 18 (1982) 997;
(b) D. Wang, Y. Fan, P. Yu, L. Désaubry, Chem. Commun. 56 (2020) 5584.
[6] (a) For reviews on furans and alkene methasis, see: V. Cadierno, P. Crochet Curr. Org. Synth. 5 (2008) 343;
(b) R. Jacques, R. Pal, N.A. Parker, C.E. Sear, P.W. Smith, A. Ribaucourt, D.M. Hodgson, Org. Biomol. Chem. 14 (2016) 5875;
(c) Castagnolo, D., in Targets in Heterocyclic Systems, Vol. 20 (Eds.: Attanasi, O. A.; Merino, P.; Spinelli, D.), 2016, p. 222–246..
[7] (a) K. Moonen, N. Dieltiens, C.V. Stevens, J. Org. Chem. 71 (2006) 4006;
(b) N. Dieltiens, K. Moonen, C.V. Stevens, Chem. Eur. J. 13 (2007) 203;
(c) M. Dolé Kerim, M. Cattoen, N. Fincias, A. Dos Santos, S. Arseniyadis, L. El Kaïm, Adv. Synth. Catal. 360 (2018) 449.
[8] M. Hermi, W. Kaminsky, C. Ben Nasr, S. Touil, Org. Prep. Proc. Int. 50 (2018) 432.
[9] H.H. Hasanov, I.K. Ivanov, V.C. Christov, Phosphorus Sulfur Silicon Relat. Elem. 193 (2018) 797.
[10] (a) L.A. Polindara-García, L.D. Miranda, Org. Lett. 14 (2012) 5408;
(b) A. Kondoh, K. Ando, M. Terada, Chem. Commun. 49 (2013) 10254;
(c) G. Flores-Constante, A.C. Sánchez-Chávez, L.A. Polindara-García, Eur. J. Org. (2018) 4586;
(c) L. Ben Gaied, N. Fincias, J. Garrec, L. El Kaïm, Eur. J. Org. (2019) 7656;
(d) K. Amiri, H. Khosravi, S. Balalaie, F. Golmohammadi, M.U. Anwar, A. Al-Harrasi, Org. Biomol. Chem. 17 (2019) 8858;
(e) M. Yildirim, G. Suleiman, Synth. Comm. 49 (2019) 463;
(e) P. Pertejo, I. Carreira-Barral, P. Peña-Calleja, R. Quesada, M. García-Valverde, J. Org. Chem. 85 (2020) 2291.
[11] B. Bernardim, E.D. Couch, A.M. Hardman-Baldwin, A.C.B. Burtoloso, A.E. Mattson, Synthesis 48 (2016) 677.
[12] S.E. Denmark, L.R. Cullen, J. Org. Chem. 80 (2015) 11818.
[13] (a) D.L.J. Clive, P. Cheng, Tetrahedron 69 (2013) 5067;
(b) V. Bhardwaj, D. Gumer, V. Abbot, S. Dhiman, P. Sharma, RSC Adv. 5 (2015) 15233;
(c) R. Kaur, V. Rani, V. Abbot, Y. Kapoor, D. Konar, K.J. Kumar, Pharm. Chem. Chem. Sci. 1 (2017) 17;
(d) , For reviews on pyrrole synthesis, see:E. Baltazzi, L.I. Krimen Chem. Rev. 63 (1963) 511;
(e) V. Estévez, M. Villacampa, J.C. Menéndez, Chem. Soc. Rev. 43 (2014) 4633.