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Alkynyltrifluoroborates as Versatile Tools in Organic Synthesis: A New Route to Spiroketals

Jan Doubský,[†] Ludvík Streinz,[†] David Šaman,[†] Jiří Zedník,[‡] and Bohumír Koutek*,[†]

The Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 166 10 Prague 6, Czech Republic, and Department of Physical and Macromolecular Chemistry, Charles University, 120 00 Prague 2, Czech Republic

koutek@uochb.cas.cz

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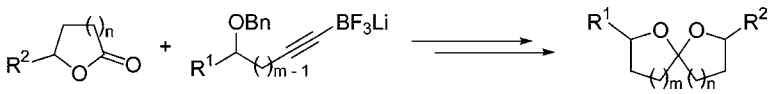
ABSTRACT



A simple and efficient two-step approach to spiroketals is described. Key steps include the preparation of functionalized hydroxyl α-alkynones by ring-opening reactions of lactones with lithium alkynyltrifluoroborates followed by a palladium-catalyzed hydrogenation/spirocyclization of the prespiroketal intermediate.

The semirigid spiroketal moiety forms a characteristic molecular element of many biologically active natural products including pheromones, marine and fungal toxins, pesticides, ionophore compounds, and polyether antibiotics. Potent biological/pharmacological activities of some representatives of this class of natural compounds combined with the synthetically challenging diverse molecular design and an extremely meager natural supply have initiated numerous target-oriented synthetic efforts.[1,2]

Among the traditional methods for spiroketal synthesis, the acid-catalyzed spiroketalization of a preformed dihydroxyketone is by far the most commonly used strategy.[1e] This well-explored approach is, however, not fully compatible with acid-labile substituents and/or protective groups in complex molecules.

Although a variety of methods leading to prespiroketal dihydroxyketone synthesis have been described, the use of acetylene derivatives as intermediates is one of the most popular routes. Numerous multistep procedures have also been devised to achieve the objective of converting protected hydroxyl α-alkynones to spiroketals. In classical conditions, each of these steps usually requires a chromatographic purification of mixtures that can be rather complex. We reasoned that a more simple strategy would be applicable to spiroketal synthesis provided that (i) straight and ready access to hydroxyl α-alkynones is available, (ii) the liberation of saturated ketodiols from protected hydroxyl α-alkynones may be integrated into the spiroketalization step by judicious choice of the protecting groups and reductive/deprotection conditions, and (iii) the spiroketalization takes place under nonacidic conditions, which could be an advantage when manipulating with acid-sensitive functionalities and would potentially give a chance to make spiroketal isomers of lower thermodynamic stability.

Herein we wish to report a methodology based on retrosynthetic Scheme 1. The key strategic elements of our approach involve the use of lithium alkynyltrifluoroborates

[†] Institute of Organic Chemistry and Biochemistry.
[‡] Charles University.

(1) For recent reviews on the synthesis of spiroketals, see: (a) Pietruszka, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2629−2636. (b) Brimble, M. A.; Farès, F. A. *Tetrahedron* **1999**, *55*, 7661−7706. (c) Tu, Y. Q.; Hübener, A.; Zhang, Hesheng; Moore, Ch. J.; Fletcher, M. T.; Hayes, P.; Dettner, K.; Francke, W.; McErlean, Ch. S. P.; Kitching, W. *Synthesis* **2000**, 1956−1978. (d) Francke, W.; Kitching, W. *Curr. Org. Chem.* **2001**, *5*, 233−251. (e) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227−256. (f) Brimble, M. A.; Furkert, D. P. *Curr. Org. Chem.* **2003**, *7*, 1461−1484.

(2) For selected recent examples of spiroketal syntheses, see: (a) Hao, J.; Forsyth, C. J. *Tetrahedron Lett.* **2002**, *43*, 1−2. (b) Sartillo-Piscil, F.; Vargas, M.; de Parrodi, C. A.; Quintero, L. *Tetraheron Lett.* **2003**, *44*, 3919−3921. (c) Tsang, K. I.; Brimble, M. A.; Bremner, J. B. *Org. Lett.* **2003**, *5*, 4425−4427. (d) Alonso, F.; Meléndes, J.; Yus, M. *Tetrahedron Lett.* **2004**, *45*, 1717−1720. (e) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569−572. (f) Ghosh, S. K.; Hsung, R. P.; Wang, J. *Tetrahedron Lett.* **2004**, *45*, 5505−5510.

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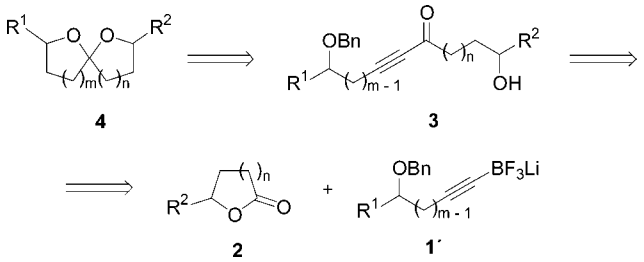
Scheme 1



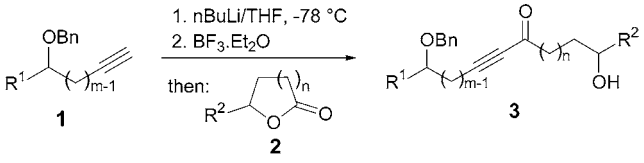
1′ to convert lactones **2** into benzyl-protected hydroxyl α-alkynones **3** followed by a one-pot cascade consisting of palladium-catalyzed hydrogenation of the triple bond, hydroxyl group deprotection, and spirocyclization under mild nonacidic conditions.

Common synthetic routes to α-alkynones include the coupling of acid chlorides, acid anhydrides, esters, and acyl cyanides with either metal (e.g., Li, Mg, Cu, Cd, Si, Ag, Zn, and Sb) acetylides or with free terminal alkynes under palladium and/or copper catalysis.[3] A few reports also exist describing the use of lithium alkynyltrifluoroborates instead of alkynyllithium reagents in coupling reactions with acid anhydrides[4] or esters.[5] Very recently, we have shown that lithium alkynyltrifluoroborates also mediate a rapid and regioselective ring opening of lactones.[6]

Thus, the synthesis of α-alkynones **3** was achieved according to our established protocol[6] via a smooth and regioselective acyl C−O ring cleavage of lactones treated with alkynyltrifluoroborates **1′** readily generated in situ from corresponding benzyl protected alkynols **1** by the addition of stoichiometric quantities of *n*BuLi and BF_3·OEt_2 in THF.

The scope of the reaction was established with a variety of alkynyltrifluoroborates using seven lactone models (Scheme 2).

Scheme 2

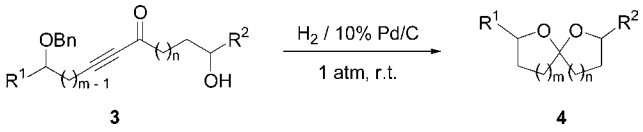


1a R^1 = H, m = 2	**2a** R^2 = H, n = 1	**3a** $R^1 = R^2$ = H, m = 2, n = 1	89%
1b R^1 = Me, m = 2	**2b** R^2 = Me, n = 1	**3b** R^1 = Me, R^2 = H, m = 2, n = 1	94%
1c R^1 = Me, m = 1	**2c** R^2 = H, n = 2	**3c** R^1 = Me, R^2 = H, m = n = 1	92%
1d R^1 = (*S*)-Me, m = 2	**2d** R^2 = H, n = 3	**3d** R^1 = (*S*)-Me, R^2 = H, m = 2, n = 1	87%
1e R^1 = H, m = 1	**2e** R^2 = Et, n = 1	**3e** $R^1 = R^2$ = Me, m = 2, n = 1	98%
	2f R^2 = *n*-Pr, n = 1	**3f** $R^1 = R^2$ = H, m = n = 2	87%
	2g R^2 = Me, n = 2	**3g** R^1 = Me, R^2 = H, m = n = 2	85%
		3h R^1 = Me, R^2 = H, m = 1, n = 2	95%
		3i R^1 = (*S*)-Me, R^2 = H, m = n = 2	83%
		3j $R^1 = R^2$ = H, m = 2, n = 3	87%
		3k R^1 = Me, R^2 = H, m = 2, n = 3	89%
		3l R^1 = H, R^2 = Et, m = n = 1	92%
		3m R^1 = Me, R^2 = *n*-Pr, m = n = 1	79%
		3n $R^1 = R^2$ = Me, m = n = 2	85%

The results shown in Scheme 2 demonstrate that this reaction sequence constitutes a highly practical alternative to frequently used α-alkynone-forming reactions. The salient features of the reaction process are (i) both starting reactants are easily available, (ii) considerable structural variation is tolerated in both the nucleophilic and electrophilic reaction components, including lactones with five-, six-, and seven-membered rings, and (iii) the reaction procedure is operationally simple and high yielding (79−98%). As expected,[7] the addition reaction could be conducted using optically active secondary alcohols (e.g., **1d**) to give optically active adducts (**3d**, **3i**).

With the requisite collection of alkynones **3** assembled, we proceeded with our investigation of the conversion **3** to **4** (Scheme 3).

Scheme 3



In our preliminary experiments, we examined the Pd/C-catalyzed hydrogenation of **3** in chloroform, anticipating that a trace of HCl liberated by a partial hydrogenolysis of the C−Cl bonds[8] might promote the hydrogenolysis of benzyl groups[9] and dehydrative ketalization as well. However, the use of $CHCl_3$ led to disappointing results. Although the procedure afforded the desired spiroketals **4** in moderate yields, it did not yield reproducible results in our hands (probably as a result of the uncontrolled activity of the Pd/C catalyst resulting in variable amounts of HCl liberated). On the other hand, a smooth and reproducible conversion of **3** to **4** was effected in a one-pot manner by treating **3** with hydrogen in the presence of 10% palladium on charcoal in EtOH or EtOAc solutions. The exploitation of these solvents is demonstrated in the synthesis of several categories of spiroketals (Table 1).

Inspection of the data in Table 1 reveals that, from the structural standpoint, the spirocyclization reaction proceeds with good generality, creating [4.4], [4.5], [5.5], and [5.6] spiroketal structures in similarly high yields (75−97%). Several other observable trends should be mentioned: (i) The rate of spiroketal formation follows approximately the order [4.4] ≈ [4.5] > [5.5] > [5.6]. (ii) Where possible, the

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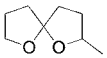
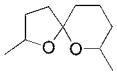
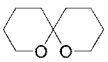
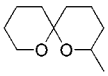
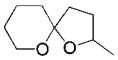
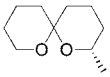
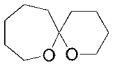
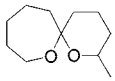
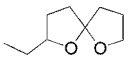
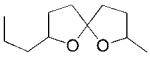
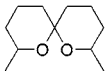
(8) Secrist, J. A.; Logue, M. W. *J. Org. Chem.* **1972**, *37*, 335−336.

Table 1. Spiroketals via the Hydrogenation/Cyclization of α-Alkynones[a]

substrate	product		isomer ratio[b]	yield[c] [%]
3a		**4a**	-	97
3b		**4b**	*E* : *Z* 7:3	78
3c		**4c**	two isomers 1:1	92
3d		**4d**	(5*S*,7*S*) : (5*R*,7*S*) 7:4	84
3e		**4e**	three isomers 1:1:2	77
3f		**4f**	-	75
3g		**4g**	*E* : *Z* 4:3	82
3h		**4h**	two isomers 1:2	81
3i		**4i**	(2*S*,6*R*) : (2*S*,6*S*) 4:3	85
3j		**4j**	-	79[d]
3k		**4k**	*E* : *Z* 3:4	91[d]
3l		**4l**	two isomers 1:1	95
3m		**4m**	four isomers 3:3:2:4	88
3n		**4n**	*E*,*E* : *E*,*Z* : *Z*,*Z* 3:5:2	76

[a] For detailed procedures, see Supporting Information. [b] Average ratio from several runs determined by GC. [c] GC yields for the sum of all isomers with hexadecane as internal standard. [d] After acidifying (the original ratio of spiroketal: hemiketal intermediate is approximately 4:3 for **4j** and 3:1 for **4k**).

spiroketals **4** are formed as an equilibrium mixture of *E* and *Z* stereoisomers that are separable by gas chromatography, while the less stable isomer is easily convertible into the thermodynamically more stable one in acidic conditions. (iii) Although the hydrogenolytic removal of benzyl protecting groups of **3** under neutral conditions gave rise in most cases to a spontaneous intramolecular ketalization process, affording the expected [4.4], [4.5], and [5.5] spiroketals **4**, the hydrogenolysis of **3j** and **3k** form an exception in that the ketalization of the preformed saturated ketodiol intermediates is not complete under these conditions leaving about 20−40% of the hemiketals noncyclized. An acidic catalyst is required to drive the cyclization reaction to completion. (iv) In the reactions of optically active hydroxyl alkynones **3d** and **3i**, the corresponding products **4d** and **4i** mirror the original stereochemistry.

The present route to spiroketals **4** certainly proceeds with considerably higher efficiency compared to that of a few previously reported methods that start from lactones[10] and involve the use of THP-protected hydroxyl-substituted alkynyllithiums,[10a,d] step by step reduction of an alkynone intermediate,[10c] or the use of cerioalkoxides.[10b] For the spiroketals in common with ours, the overall yields (% from lactones) found in the literature and in this work are, respectively, **4a**, 7.5,[10a] 69,[10b] and 86; **4b**, 22[10a] and 73; **4c**, 25[10a] and 85; **4d**, 27[7] and 73.1; **4e**, 36[10a] and 75; **4h**, 21[10a] and 77; **4l**, 37,[10a] 63,[7] and 87; **4j**, 49[10b] and 69.

In conclusion, we have shown that it is possible to convert lactones into a range of spiroketals in two steps via alkynyltrifluoroborate chemistry. While minimizing protecting group manipulations, both reaction steps proceed with high yields, thus adding a simple and scalable method for accessing spiroketal motifs within natural product frameworks. Work to extend this methodology to other (chiral lactone) substrates, kinetics of the less stable isomer formation, detailed studies of NMR spectra, and the preparation of more sophisticated targets is underway.

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Supporting Information Available: Experimental procedures for the synthesis of alkynones **3** and their one-pot transformation to spiroketals **4**, selected analytical data, and examples of GC−MS, GC−IR, and NMR spectra for important compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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