ORGANIC LETTERS

2006
Vol. 8, No. 8
1633−1636

The Silylalkyne-Prins Cyclization: Stereoselective Synthesis of Tetra- and Pentasubstituted Halodihydropyrans

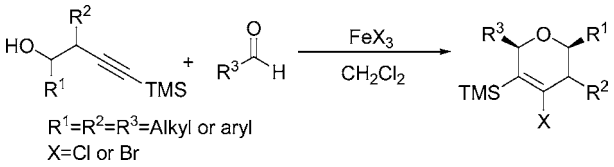
Pedro O. Miranda, Miguel A. Ramírez, Víctor S. Martín,* and Juan I. Padrón*

Instituto Universitario de Bio-Orgánica "Antonio González", Universidad de La Laguna, C/Astrofisico Francisco Sánchez 2, 38206 La Laguna, Tenerife, Spain

jipadron@ull.es; vmartin@ull.es

Received January 27, 2006

ABSTRACT



A new type of Prins cyclization using silylated secondary homopropargylic alcohols and aldehydes yielding tetra- and pentasubstituted dihydropyrans is described. The presence of the trimethylsilyl group in the triple bond favors the Prins cyclization and minimizes the 2-oxonia-[3,3]-sigmatropic rearrangement as a competitive alternative pathway. Ab initio theoretical calculations of the species involved in the rearrangements support the proposed mechanism. The process is highly stereoselective, affording *cis*-dihydropyran as the only isomer.

The Prins cyclization is a powerful tool to obtain substituted tetrahydropyrans.[1,2] When homoallylic alcohols or α-acetoxy ethers are used to generate the oxocarbenium ion intermediate, an oxonia-Cope rearrangement can take place as a competitive process with the Prins cyclization (Figure 1). When enantiomeric chiral starting materials are used, this rearrangement occasionally becomes deleterious to the Prins cyclization, giving a partial or total racemization.[1d,f,3] A full study including factors to modulate these competitive processes has been recently reported by Rychnovsky et al.[2f]

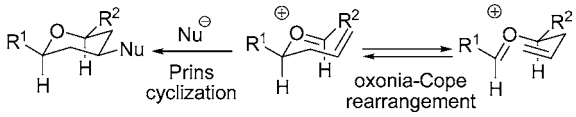


Figure 1. Prins cyclization and oxonia-Cope rearrangement.

We have found a new Prins-type cyclization between homopropargylic alcohol and aldehydes in the presence of inexpensive, environmentally friendly, and stable iron(III) halides to obtain 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans **4** ($R^1 = R^2 = R^4 = H$).[4] However, when secondary homopropargyllic alcohols were used the reaction proceeded by a domino

(1) (a) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661−672. (b) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092−1093. (c) López, F.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 4218−4219. (d) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815−3818. (e) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919−3922. (f) Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429−2432.

(2) For recent examples in the use of Prins reaction, see: (a) Dobbs, A. P.; Guesné, J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880−7883. (b) Yadav, V. K.; Kumar, N. V. *J. Am. Chem. Soc.* **2004**, *126*, 8652−8653. (c) Rychnovsky, S. D.; Dalgard, J. E. *J. Am. Chem. Soc.* **2004**, *126*, 15662−15663. (d) Yu, C.-M.; Yoon, S. K.; Hong, Y. T.; Kim, J. *Chem. Commun.* **2004**, 1840−1841. (e) Overman, L. E.; Velthuisen, E. J. *Org. Lett.* **2004**, *6*, 3853−3856. (f) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem Soc.* **2005**, *127*, 9939−9945 and references therein. (g) Chan, K.-P.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 4491−4494.

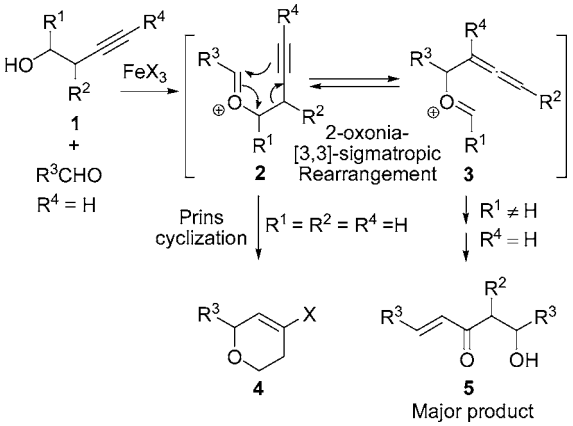
(3) (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett*, **2002**, *4*, 577−580. (b) Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, R. A.; Parker, G. D.; Roe, R.; Willis, C. L. *Chem. Commun.* **2005**, 3727−3729.

(4) (a) Miranda, P. O.; Diaz, D. D.; Padrón, J. I.; Bermejo, J.; Martín, V. S. *Org. Lett.* **2003**, *11*, 1979−1982. (b) Miranda, P. O.; Diaz, D. D.; Padrón, J. I.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **2005**, *70*, 57−62.

10.1021/ol060247m CCC: $33.50
Published on Web 03/25/2006

sequence through an allenolate formation, further 1,3-O-transposition, and enolate coupling leading to unsaturated β-hydroxy ketones **5** as the main products. In this sequence, an oxonia-[3,3]-sigmatropic rearrangement over the oxocarbenium ion **2**, as competitive alternative pathway to the Prins cyclization, leads to the key allenolate **3** (Scheme 1).[5] The

Scheme 1. Coupling of Homopropargylic Alcohols and Aldehydes Catalyzed by Iron(III) Halides



course of the reaction (rearrangement or Prins type cyclization) depends directly on the stability of the species involved in this rearrangement.

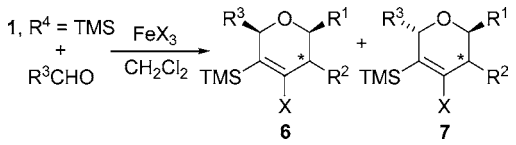
Considering the well-documented silyl-modified Prins cyclization,[6] we decided to explore the introduction of a trimethylsilyl group in the triple bond (R^4 = TMS), as a way to minimize the 2-oxonia-[3,3]-sigmatropic rearrangement in the above-mentioned equilibrium.[7]

In this paper, we describe a new, general, and stereoselective method to obtain tetra- and pentasubstituted dihydropyrans based on an alkyne silyl-Prins cyclization catalyzed by iron(III) halides. Ab initio theoretical calculations of the species involved in the rearrangement support our results and the proposed mechanism.

First, to test the scope of FeX_3 in this coupling reaction, we carried out the reaction between secondary trimethylsilyl propargyllic alohols (**1**, R^4 = TMS, $R^2 \neq$ H) and several aldehydes using $FeCl_3$ and $FeBr_3$[8] as promoters.[9] Table 1 summarizes the results obtained in this study.

The methodology produced exclusively and in good yield the desired six-membered rings. No traces of the products resulting from the oxonia rearrangement were observed. The

Table 1. Silylalkyne-Prins Cyclization of Secondary Trimethylsilyl Homopropargylic Alcohols and Aldehydes Using FeX_3 as a Promoter



entry	R^1	R^2	R^3	X	**6/7**	yield (%)
1	Me	H	*i*-Bu	Cl	50:50	80
2	Me	H	*c*-C_6H_{11}	Cl	>99:1[c]	65
3	Me	H	Ph	Cl		
4	Me	H	*s*-Bu	Cl	>99:1[c]	82
5	Me	H	*s*-Bu	Br	>99:1[c]	75
6	Et	H	*c*-C_6H_{11}	Cl	>99:1[c]	75
7	Bn	H	*c*-C_6H_{11}	Cl	>99:1[c]	57
8	*c*-C_6H_{11}	H	*c*-C_6H_{11}	Cl	>99:1[c]	55
9	*c*-C_6H_{11}	H	Bn	Cl	>99:1[c]	61
10[a]	Me	Me	$Br_2C{=}CH(CH_2)$-	Cl	>99:1[c]	60
11[b]	Me	Me	*c*-C_6H_{11}	Cl	>99:1[c]	62

[a] Racemic (2*R**,3*R**)-3-methyl-5-(trimethylsilyl)pent-4-yn-2-ol was used as **1**. [b] Racemic (2*S**,3*R**)-3-methyl-5-(trimethylsilyl)pent-4-yn-2-ol was used as **1**. [c] Within the NMR detection limit, **7** was not observed.

reaction works well with a wide range of aldehydes except benzaldehyde (entry 3). However, other aldehydes containing aromatic rings, although located on a distal position relative to the carbonyl group, proceeded satisfactorily (entry 9).

The presence of the silyl group at the alkyne is essential to achieve the reaction since when the acetylene is substituted with a methyl group the process is inhibited. In addition, the size of the substituent at the silicon atom is also a critical factor. For instance, when the triple bond bears a triisopropyl silyl group instead of TMS, the reaction does not take place.

The alkyne silyl-Prins reaction proceeds at room temperature and with complete diastereocontrol, obtaining exclusively the *cis*-2,6-dihydropyran product. An exception was found for 3-methylbutanal (entry 1).

With this methodology in hand, we can access tetra- and pentasubstituted dihydropyrans in one step using the suitable secondary trimethylsilyl homopropargylic alcohol. The alkyne-Prins cyclization worked in good yields, leading to the pentasubstituted dihydropyrans, when 3-methyl-5-(trimethylsilyl)pent-4-yn-2-ol was used as starting material (entries 10 and 11).

To account for the stereochemical course of the reaction, "ab initio" theoretical calculations at the B3LYP/6-31G(d) level were performed for some cases of **6** and **7** (Table 2). The calculations showed that the *cis* stereoisomers **6** are always more stable than *trans* isomers **7**. The small energetic difference for both stereoisomers when R^3 = *i*-Bu accounts for the only exception (50:50) (Table 1, entry 1) relative to the general stereochemical course of the reaction.

As pointed out above, the presence of the trimethylsilane is essential to generate the corresponding dihydropyran. Surprisingly, the obtained halosilylalkene proved to be a very unreactive system. For instance, all standard conditions

(5) Miranda, P. O.; Ramírez, M. A.; Padrón, J. I.; Martín, V. S. *Tetrahedron Lett*. **2006**, *47*, 283−286.

(6) Silyl-modified Prins cyclization: (a) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem*. **1997**, *62*, 3426−3427. (b) Viswanathan, G.; S.; Yang, J.; Li, C.-J. *Org. Lett*. **1999**, *1*, 993−995.(c) Dobbs, A. P.; Martinovic, S. *Tetrahedron Lett*. **2002**, *43*, 7055−7057. (d) Dobbs, A. P.; Guesne, S. J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem*. **2003**, *68*, 7880−7883. (c) Meilert, K.; Brimble, M. A. *Org. Lett*. **2005**, *7*, 3497−3500.

(7) Lee, K.-C.; Lin, M.-J.; Loh, T.-P. *Chem. Commun*. **2004**, 2456−2457.

(8) $FeCl_3$ and $FeBr_3$ were purchased form the Aldrich Chemical Co.

(9) For availability or synthesis of **1**, see the Supporting Information.

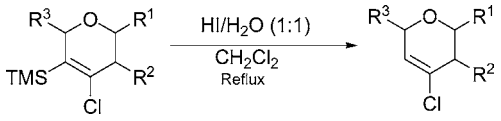
Table 2. Ab Initio Calculations of Some *cis*- and *trans*-2-Alkyl-4-chloro-6-methyl-5,6-dihydro-2*H*-pyran-3-yl)-trimethylsilanes

entry	R^1	R^2	R^3	$E_{cis} - E_{trans}$[a] (kcal/mol)
1	Me	H	*i*-Bu	−0.6
2	Me	H	*c*-C_6H_{11}	−3.8
3	Me	H	*s*-Bu	−2.5

[a] **6** (*cis*) and **7** (*trans*) were fully optimized at B3LYP/6-31G(d) level "ab initio" calculation.

assayed to cleave the C−Si bond proved fruitless.[10] Fortunately, the cleavage of the TMS group was satisfactorily achieved under aqueous iodhydric acid[11] refluxing for 1 week. Besides the long reaction time period, the corresponding desilylated dihydropyrans were obtained in excellent yields with complete retention of the *cis* or *trans* configuration (Table 3).

Table 3. Desilylation of the Tetra- and Pentasubstituted Dihydropyrans. Synthesis of 2,6-Dialkyl-4-chloro-5,6-dihydro-2*H*-pyrans



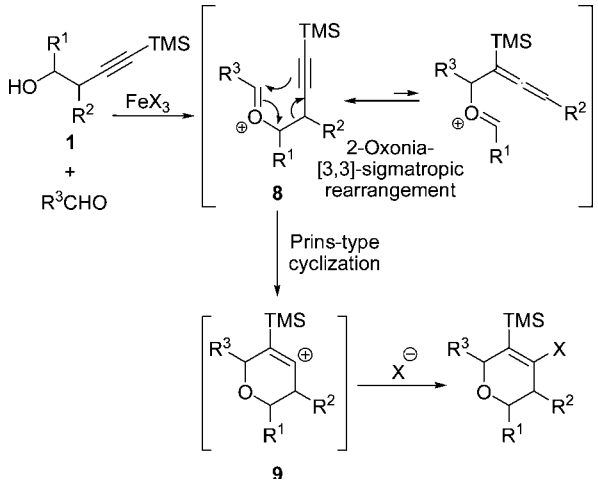
entry	R^1	R^2	R^3	*cis* or *trans*	yield (%)
1	Me	H	*i*-Bu	*cis*	88
2	Me	H	*i*-Bu	*trans*	87[a]
3	Me	H	*c*-C_6H_{11}	*cis*	86
4	Me	Me	*c*-C_6H_{11}	*cis*	92

[a] The reflux period was extended to 2 weeks.

A plausible mechanism for this new alkyne silyl-Prins cyclization is outlined in Scheme 2. The reaction of the secondary silyl-homopropargylic alcohol and an aldehyde promoted by ferric halide generates the oxocarbenium ion **8**.[4] This intermediate evolves to the corresponding-DHP, via the silicon-stabilized β-carbocation **9**.[12]

To provide further evidence of the proposed mechanism, "ab initio" theoretical calculations at the B3LYP/6-31G(d) level were performed on simplified structures. The results of these calculations are summarized in the energy diagrams shown in Figure 2. The rearrangement with silicon is less favored than without silicon. Thus, the α-silane allenyl cation **12** is 5.70 kcal/mol less stable than **10**, which indicates that this rearrangement is not favored. In addition, the silyl cation **11** is 7.71 kcal/mol less stable than its open form **10**, which could be the intermediate toward the Prins cyclization.[13] On

Scheme 2. Proposed Mechanism for the Addition of Secondary TMS-Homopropargylic Alcohols and Aldehydes



the other hand, the suppression of the silyl group in the alkynyl carbocation **13** leads to the 3.24 kcal/mol more stable allenyl carbocation **14**. This energy profile correlates very well with our proposed mechanism.

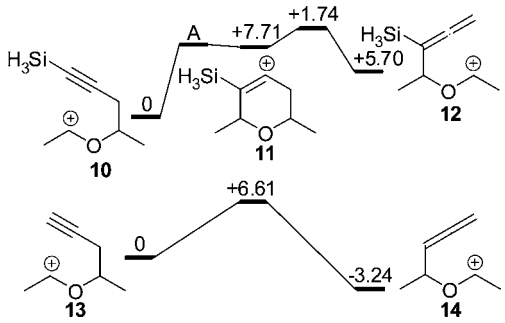


Figure 2. Energy (kcal/mol) profile of 2-oxonia-[3,3]-sigmatropic rearrangements.

Interestingly, we were unable to locate a dihydropyranyl cation intermediate for the alkynyl carbocation ion **13**, presumably indicating a concerted pathway to **14**.

To confirm that no racemization was occurring during the cyclizations to the tetrasubstituted dihydropyrans, (*R*)-1-cyclohexyl-4-(trimethylsilyl)but-3-yn-1-ol (93% ee)[14] was treated with 2-phenylacetaldehyde and $FeCl_3$. The corresponding dihydropyran **16** (86% ee) shows a slightly reduced but still synthetically useful enantiopurity compared to the starting homopropargylic alcohol (*R*)-**15** (93% ee) (Scheme 3). This small difference may be due either to a fast equilibrium between the favored cationic species such as **11**

(10) Desilylation conditions tested: TBAF/THF, HF/CH_3CN, I_2/H_2O/CH_2Cl_2 refluxing.

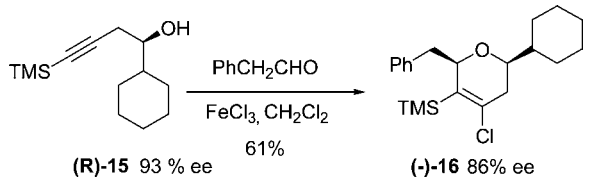
(11) Mayr, H.; Bäuml, E.; Cibura, G.; Koschinsky, R. *J. Org. Chem.* **1992**, *57*, 768−772.

(12) Siehl, H.-U. *Pure Appl. Chem.* **1995**, *67*, 769−775.

(13) A transition state **A** of close energy to the silyl cation intermediate **11** should exist.

(14) The (*R*)-1-cyclohexyl-4-(trimethylsilyl)but-3-yn-1-ol was prepared in seven steps (32% overall yield, 93% ee) from (*E*)-3-cyclohexylprop-2-en-1-ol. See the Supporting Information.

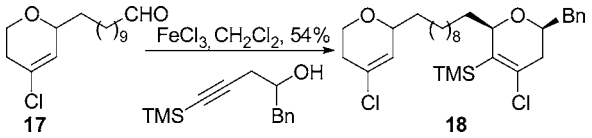
Scheme 3. Cyclization of Enantioenriched Homopropargylic Alcohol



and the allenic form **12**, or may even be caused by experimental error during the measurement.

Finally, to explore the synthetic scope of this method we decided to perform the synthesis of a tetrasubstituted dihydropyran from the more elaborated and non commercial aldehyde **17**.[15] The unprecedented dimer-type **18** was obtained in 54% yield, showing that this new methodology could be applied to the synthesis of complex molecules in a highly efficient and convergent manner (Scheme 4).

Scheme 4. Synthesis of a Tetrasubstituted Dihydropyran Dimer Type



In conclusion, we report on a new stereoselective method to obtain tetra- or penta substituted halo-dihydropyrans, avoiding the reactions derived from a competitive 2-oxonia-[3,3]-sigmatropic rearrangement. The coupling between chiral secondary homopropargylic alcohols bearing a trimethylsilyl group at the triple bond and aldehydes in the presence of iron(III) halides, provides (2,5,6-trialkyl-4-halo-5,6-dihydro-*2H*-pyran-3-yl)trimethylsilane in good yields maintaining the enantiopurity of the starting material at a very good level. Ab initio theoretical calculations support the proposed mechanism and show that the sigmatropic rearrangement is not a serious competitive pathway providing the secondary homopropargylic alcohol is silylated at the triple bond. Synthetic applications of this new methodology to the synthesis of other natural compounds are under study and will be published in due course.

Acknowledgment. This research was supported by the Ministerio de Educación y Ciencia of Spain, co-financed by the European Regional Development Fund (CTQ2005-09074-C02-01/BQU) and the Canary Islands Government. P.O.M. thanks the Spanish M.E.C. for a F.P.I. fellowship. J.I.P. thanks the Spanish MCYT-F.S.E. for a Ramón y Cajal contract.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060247M

(15) The noncommercial aldehyde **17** was prepared in three steps (51% overall yield) from the alkyne Prins cyclization of but-3-yn-1-ol and 11-bromoundecanal. See the Supporting Information.