ORGANIC LETTERS

2003
Vol. 5, No. 11
1979−1982

Iron(III)-Catalyzed Prins-Type Cyclization Using Homopropargylic Alcohol: A Method for the Synthesis of 2-Alkyl-4-halo-5,6-dihydro-2*H*-pyrans

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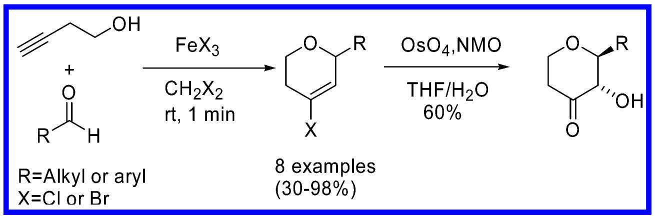
Received April 1, 2003

ABSTRACT



A new Prins-type cyclization between homopropargylic alcohol and aldehydes in the presence of FeX$_3$ to obtain 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans in good yield is described. Osmium-catalyzed cis dihydroxylation provided direct access to *trans*-2-alkyl-3-hydroxy-tetrahydropyran-4-ones. Anhydrous ferric halides are also shown to be excellent catalysts for the standard Prins cyclization using homoallylic alcohol. Isolation of an intermediate acetal provides substantiation of a proposed mechanism.

Medium-sized oxacycles constitute important synthetic targets due to the fact that they form the structural cores of numerous natural products.[1] The dihydropyran skeleton of these molecules is particularly attractive since the olefin function is a synthetically useful handle for further functionalization in obtaining polysubstituted tetrahydropyrans.[2,3] The possibility of obtaining, in a single step, a functionalized heterocyclic ring in the field of natural products is an ardently pursued objective.

The coupling between olefins and aldehydes induced by Lewis acid, known as the *Prins* reaction,[4] to generate tetrahydropyran derivatives has been extensively applied to synthesize many natural products containing cyclic polyethers in their structures.[5,6] Cyclic or mixed acetals and α-acetoxy ethers are useful intermediates for generating the oxocarbenium ions of the Prins cyclization.[7]

As a result of our studies directed toward the synthesis of marine natural compounds containing six-membered oxa-

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(1) For comprehensive reviews, see: (a) Oishi, T.; Ohtsuka, Y. In *Studies in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam 1989; Vol. 3, p 73. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007.

(2) For a review, see: Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309−3362.

(3) For examples of synthesis of polysubstituted tetrahydropyrans and dihydropyrans, see: (a) Coppi, L.; Ricci, A.; Tadei, M. *J. Org. Chem.* **1988**, *53*, 913−915. (b) Li, C.-J.; Zhang, W.-C. *Tetrahedron* **2000**, *56*, 2403−2411. (c) Schmidt, B.; Westhus, M. *Tetrahedron* **2000**, *56*, 2421−2426.

(4) (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505−555 (b) Snider, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 527−561.

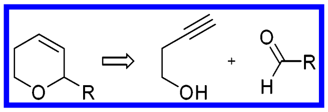
(5) (a) Stapp, P. R. *J. Org. Chem.* **1969**, *34*, 479−485. (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661−672. (b) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092−1093 and references therein.

(6) For recent advances in the *Prins* reaction, see: (a) López, F.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 4218−4219. (b) Camara, C. A.; Pinto, A. C.; Vargas, M. D.; Zukerman-Schpector, J. *Tetrahedron* **2002**, *58*, 6135−6140. (c) Cho, Y. S.; Kim, H. Y.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Chang, M. H. *Org. Lett.* **2002**, *4*, 2025−2028. (d) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815−3818.

10.1021/ol034568z CCC: $25.00

cycles,[8] we addressed our attention to the Prins cyclization as a way of obtaining dihydropyrans (Scheme 1).[9] In our approach and considering precedents found in the literature using the intramolecular cyclization of acetals, we pondered the possibility of the direct coupling of homopropargylic alcohol and aldehydes[10] as molecular fragments.[7]

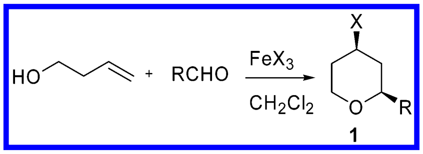
Scheme 1



Within the Lewis acid catalog, $FeCl_3$ is an inexpensive, environmentally friendly, and stable Lewis acid. Herein, we report on a Prins cyclization for accessing 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans that make use of the direct coupling of homopropargylic alcohol and aldehydes induced by anhydrous ferric halides ($FeCl_3$ and $FeBr_3$). We also found that such intermediates are useful substrates, for example, to stereoselectively obtain 2-alkyl-3-hydroxy-tetrahydropyran-4-one as a single diastereoisomer after a cis dihydroxylation reaction.

First, to check the catalytic behavior of FeX_3 in the Prins cyclization, we carried out the reaction between 3-buten-1-ol and several aldehydes using such Lewis acids as a promoter. $FeCl_3$ and $FeBr_3$[11] showed that the cyclization proceeded satisfactorily, affording the corresponding *cis*-4-halo-2-alkyl tetrahydropyrans **1**[12] in good yields.[3a] Table 1 summarizes the results obtained in this study.[13] The reaction works very well with both aliphatic and aromatic aldehydes. A moderate yield was obtained only in the case of an aldehyde with a hydroxy-substituted aromatic ring (entry 5).

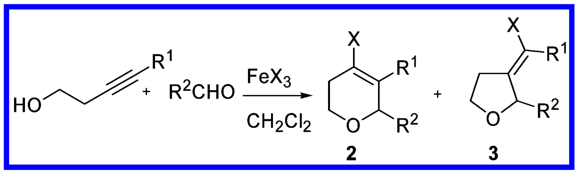
Table 1. Cyclization of Homoallyl Alcohol and Aldehydes Using FeX_3 as a Promoter



entry	R	X	yield (%)
1	*c*-C_6H_{11}	Cl	90
2	*i*-Bu		93
3	Ph		97
4	*p*-NO_2Ph		83
5	*p*-HOPh		48
6	*c*-C_6H_{11}	Br	93
7	Ph		90
8	1-naphthyl		97

With these results in hand, we extended our studies using homopropargylic alcohol instead of homoallylic alcohol.[14] We obtained the corresponding 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans **2** in good yields (Table 2).[15]

Table 2. Synthesis of 2-Alkyl-4-halo-5,6-dihydro-2*H*-pyrans from Homopropargylic Alcohol and Aldehydes Using FeX_3 as a Catalyst



entry	R^1	R^2	X	2:3	yield (%)
1	H	*c*-C_6H_{11}	Cl	100: 1	80
2		*i*-Bu			90
3		Ph			30
4		Bn			75
5		*i*-Bu	Br	[a]	98
6		*c*-C_6H_{11}		[a]	93
7		Bn		[a]	92
8	Me	*n*-C_6H_{12}	Cl	35:65	80

[a] Product was contaminated with the corresponding chlorovinyl derivative (see text and Scheme 2).

The methodology produced in a good yield the desired six-membered ring with a wide range of aldehydes except when benzaldehyde was used (entry 3).[16] However, other aldehydes containing aromatic rings, although located in a distal position (entries 4 and 7) relative to the carbonyl group, proceeded satisfactorily. When pent-3-yn-1-ol was used

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[7] (a) Sano, T.; Oriyama, T. *Synlett* **1997**, *6*, 716−718. (b) Bunnelle, W. H.; Seamon, D. W.; Mohler, D. L.; Ball, T. F.; Thompson, D. W. *Tetrahedron Lett.* **1984**, *25*, 2653−2654. (c) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679−4686, and references therein.

[8] (a) Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Palazón, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570−4583. (b) Ramírez, M. A.; Padrón, J. M.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 4584−4590. (c) Betancort, J. M.; Martín, T.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **2003**, *68*, 3216−3224.

[9] For the synthesis of dihydropyrans using the Prins cyclization, see: (a) Viswanathan, G. S.; Yang, J.; Li, C.-J. *Org. Lett.* **1999**, *1*, 993−995. (b) Dobbs, A. P.; Martinović, S. *Tetrahedron Lett.* **2002**, *43*, 7055−7057.

[10] For precedents in the direct coupling of aldehydes and acetylenes yielding nitrogen heterocycles, see: Lin, N.-H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062−9072 and references therein.

[11] $FeCl_3$ and $FeBr_3$ were purchased from the Aldrich Chemical Co.

[12] Stereochemistry was determined by NOE studies. See Supporting Information.

[13] To the best of our knowledge, this is the first report on the use of Fe(III) halides promoting the Prins reaction.

[14] For a coupling of homopropargylic alcohol with aldehydes yielding allylic alcohols, see: Takai, K.; Sakamoto, S. Isshiki, T. *Org. Lett.* **2003**, *5*, 653−655.

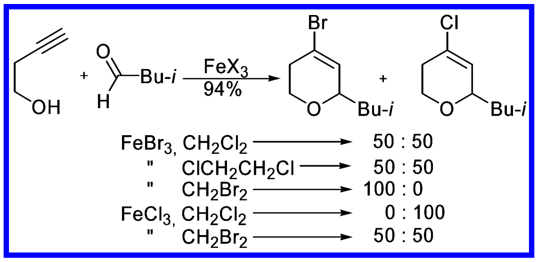
[15] For precedents in the synthesis of halovinyl tetrahydropyrans, see: (a) Melany, M. L.; Lock, G. A.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 3925−3927. (b) Chan, T. H.; Arya, P. *Tetrahedron Lett.* **1989**, *30*, 4065−4068. (c) Tsukayama, M.; Utsumi, H.; Kunugi, A.; Nozaki, H. *Heterocycles* **1997**, *45*, 1131−1142.

[16] **Typical Experimental Procedure for a Ferric Halide Promoted Prins Cyclization.** To a solution of homoallylic alcohol or homopropargylic alcohol (1 equiv) and aldehyde (1 equiv) in dry CH_2Cl_2 was added anhydrous FeX_3 (1 equiv) in one portion. The reaction was complete in approximately 1 min, quenched by addition of water with stirring for 5 min, and extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems).

(entry 8), the tetrahydrofuran **3** was the major cyclic product.[7b] With other alkyne alcohols such as 4-pentyn-1-ol and 5-hexyn-1-ol, no cyclization reaction was observed.[17]

From the different solvents screened (THF, CH_3CN, AcOEt, $CHCl_3$, CCl_4, CH_3NO_2, CH_2Cl_2, and 1,2-dichloroethane) we found the best conditions using CH_2Cl_2 and 1,2-dichloroethane. However, an unexpected result was the appearance of chlorovinyl derivatives when $FeBr_3$, in CH_2Cl_2, was used as a catalyst. In an attempt to clarify this point, we ran a reaction using 1,2-dichloroethane as a solvent and obtained a similar amount of the chloro dihydropyran. Our suspicion that the chlorine atom comes from the solvent was clarified by the use of CH_2Br_2 as a solvent, when the uncontaminated bromovinyl ring was cleanly obtained. In a similar manner, the use of $FeCl_3$ in CH_2Br_2 produced the chloro derivative contaminated with the corresponding bromide (Scheme 2). In addition, we did not find any contamination when the Prins cyclization was performed over allylic alcohol (Table 1). Although at the moment we do not have a clear explanation for these facts, two alternatives in consideration are some halide exchange with the halogenated solvent in the metal[18] or the capture of the solvent halogen by the vinyl cation intermediate.[19] From the synthetic point of view, it is clear that for each halide the corresponding halogenated solvent must be used.

Scheme 2



To clarify the structure of the obtained cyclic compounds, we performed a series of chemical transformations that also showed the synthetic versatility of such intermediates (Scheme 3). Thus, **2** (R^1 = H, R^2 = C_6H_{11}-*c*) was hydrogenated using Pd/C as a catalyst to give the tetrahydropyran **4**, which was also synthesized by reductive elimination of 4-chloro-2-alkyl-tetrahydropyran **1** obtained by coupling between homoallylic alcohol and aldehyde in the presence of $FeCl_3$. On the other hand, reductive ozonolysis of **2** provided the aldehyde **5** that supports the presence of the six-membered ring. When the halovinyl tetrahydropyrans **2** were submitted to osmium-catalyzed cis hydroxylation, the *trans*-2-alkyl-3-hydroxy-tetrahydro-pyran-4-ones **6** were stereoselectively produced as the sole stereoisomer.[12] Although the isolated yields are modest, the procedure implies only one step and that the reaction is clean inasmuch as only one spot is detected by TLC.[20]

Scheme 3

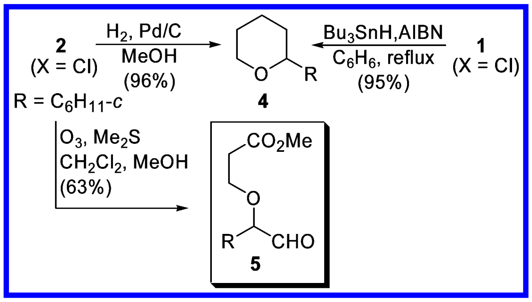
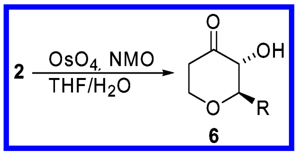


Table 3. Cis Hydroxylation of 2-Alkyl-4-halo-5,6-dihydro-2*H*-pyrans



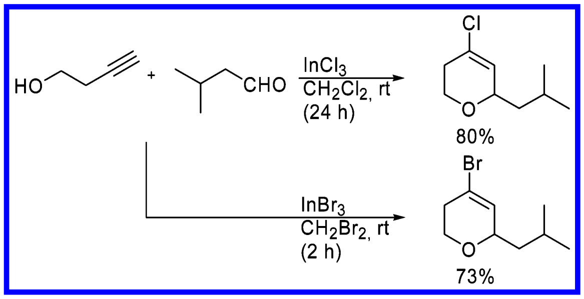
entry	R, X	time (60 °C)[a]	yield
1	*c*-C_6H_{11}, Cl	3 days	59
2	*i*-Bu, Cl	3 days	56
3	Ph, Cl	3 days	60
4	Bn, Cl	3 days	60
5	Bn, Br	3 days	56

[a] At room temperature, the completion of the reaction requires 7 days and additional OsO_4 must be added at approximately 50% conversion.

To optimize the reaction conditions, the amount of anhydrous ferric chloride was also varied from catalytic to 3 equiv, and it was found that the highest yields were obtained when 1 equiv was used. A noteworthy aspect of the reaction is that the carbon−carbon formation is very rapid even at 0 °C and is usually completed within 1 min.[21]

To check the advantage of the use of iron over other metal halides, we performed a few runs using indium halides as catalysts (Scheme 4).[22] We found that both $InCl_3$ and $InBr_3$ also induced the cyclization of propargylic alcohol and aldehydes to the corresponding dihydropyrans, but

Scheme 4



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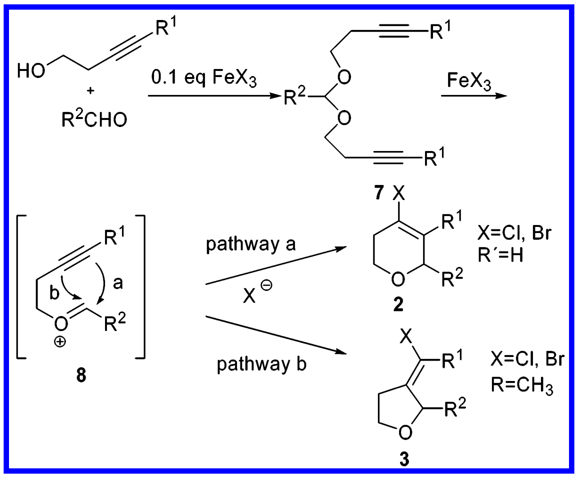
[17] All compounds were satisfactorily characterized by elemental analyses (±0.4% for C, H, etc.) and spectral data (IR, ^1H NMR, and ^{13}C NMR). See Supporting Information.

the reactions are slower and the yields obtained are slightly lower.

Using a catalytic amount of $FeCl_3$ (0.1 equiv), we obtained the acetal **7** as a single product in a good yield (80%). The intermediate acetal was isolated and fully characterized and, when treated with more ferric chloride to reach 1 equiv, yielded cleanly the halovinyl tetrahydropyran.[7a] A plausible mechanism involves the acetal **7** that, via FeX_3-mediated ionization, generates the oxonium ion **8** that is intramolecularly trapped by the triple bond with concomitant attack of the halide (Scheme 5).

Scheme 5



In conclusion, we report a novel use of iron(III) halides as efficient catalysts for Prins cyclizations. The coupling between homopropargylic alcohols and aldehydes provides 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans in good yields. The reaction is applicable to both aromatic and aliphatic substrates, as well as with both enolizable and nonenolizable aldehydes. A new synthesis of *trans*-2-alkyl-3-hydroxy-tetrahydro-pyran-4-ones is described. Efforts in the application of the developed methodologies to the synthesis of highly functionalized tetrahydropyrans are currently underway in our laboratory and will be published in due course.

Acknowledgment. This research was supported by the Ministerio de Ciencia y Tecnologia (PPQ2002-04361-C04-02) and the Canary Islands Government. D.D. thanks the Spanish M.E.C. for a F.P.I. fellowship. Many thanks are also given to Dr. Sreenivas Punna for useful discussions and suggestions.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds and COSY and NOE experiments for compounds **1** (R = C_6H_{11}-*c*) and **6** (R = C_6H_{11}-*c*). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For a precedent about the halogen transfer from halogenated solvents to a metal, see: Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem. Eur. J.* **2001**, *7*, 5299−5317.

(19) This alternative could explain why the halide exchange does not occur in the homoallylic alcohols (Table 1).

(20) At the moment, we cannot determine the fate of the remainder of the matter.

(21) Reaction has been scaled up to 5 g with no difficulty.

(22) For the use of InX_3 in Prins reactions, see refs 6c and 9b. The use of $InBr_3$ in CH_2Cl_2 produces a 7:3 mixture of bromo and chloro dihydropyran derivatives.