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In situ generation of 2,3-allenolates in the coupling of secondary homopropargylic alcohols and aldehydes

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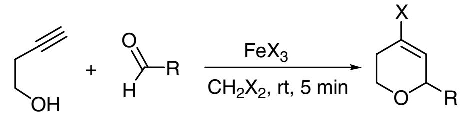
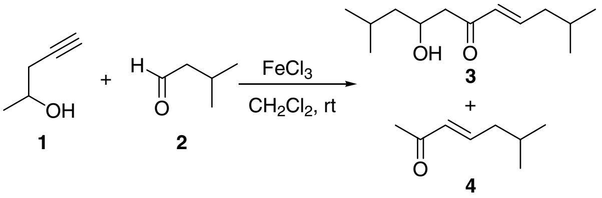
Abstract—A study on a novel oxonia [3,3]-sigmatropic rearrangement as competitive alternative pathway to the acetylenic Prins cyclization on the addition of secondary homopropargylic alcohols to aldehydes catalyzed by iron(III) is described. 'Ab initio' theoretical calculations of the species involved on the rearrangement supports the in situ formation of 2,3-allenolates. The domino process involves three consecutive chemical events in one-pot format reaction (~70% average).

In continuation of our research program directed toward the synthesis of marine natural compounds containing six-membered oxacycles,[1] we addressed our attention toward the Prins cyclization[2,3] promoted by the inexpensive, environmentally friendly, and stable iron(III) halides, as a way to obtain 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans (Scheme 1).[4]

Extending our previous work, we explored such methodology for the synthesis of 2,6-disubtituted dihydropyrans using secondary homopropargylic alcohols. Surprisingly the treatment of pent-4-yn-2-ol (**1**, $R^1 = R^4 = H$, $R^2 = Me$) and 3-methylbutanal (**2**, $R^3 = i$-Bu) in the presence of $FeCl_3$ led to unsaturated (*E*)-β-hydroxyketone **3** and (*E*)-α,β-unsaturated ketone **4** in 2.5:1 ratio and 65% yield, without any trace of the expected Prins-type cyclic product (Scheme 2).



Scheme 1. Synthesis of 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans.



Scheme 2. Coupling of secondary homopropargylic alcohols and aldehydes catalyzed by iron(III) halides.

Precedents for the synthesis of these type of compounds making use of allenol as starting material have been reported from the laboratories of Trost[5] and Yu[6] using vanadium and indium as catalysts, respectively.

Herein, we report a study on a novel oxonia [3,3]-sigmatropic rearrangement as competitive alternative pathway to the alkyne Prins cyclization resulting on the addition of secondary homopropargylic alcohols to aldehydes catalyzed by iron(III). Ab initio theoretical calculations of the species involved in the rearrangement as well as experimental evidence support the in situ formation of key allenolates (Scheme 3).[7]

Firstly to test the scope of FeX_3 in this coupling reaction, we carried out the reaction between pent-4-yn-2-ol (**1**, $R^1 = R^4 = H$, $R^2 = Me$) and several aldehydes using $FeCl_3$ and $FeBr_3$[8] as promoters. Table 1 summarizes the results obtained in this study.[9]

Keywords: [3,3]-Sigmatropic rearrangement; Prins cyclization; Iron(III) halides.

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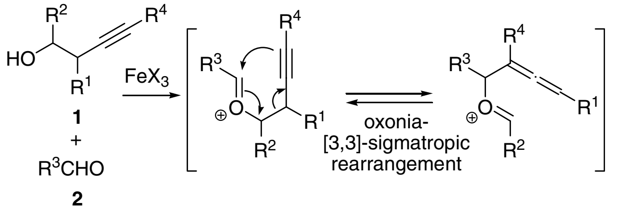
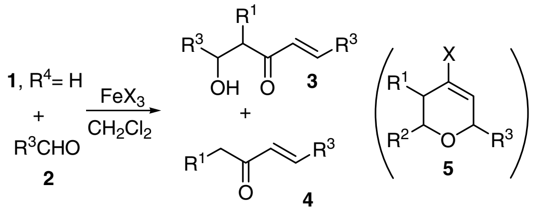


Scheme 3. Oxonia-[3,3]-sigmatropic rearrangement during the coupling of secondary homopropargylic alcohols and aldehydes.

Table 1. Addition of secondary homopropargylic alcohols and aldehydes using FeX_3 as promoter



Entry	R^1	R^2	R^3	X	**3**:**4**	Yield (%)
1	H	Me	*n*-C_6H_{13}	Cl	7:3	70
2	H	Me	*i*-Bu	Cl	7:3	65
3	H	Me	*t*-Bu	Cl	10:0	40
4	H	Me	Ph	Cl	10:0	12
5	H	Me	*c*-C_6H_{11}	Cl	3:2:5[a]	60
6	Me	Me	*i*-Bu	Cl	9:1[b]	40
7	H	Me	*n*-C_6H_{13}	Br	10:0	44
8	H	Me	*i*-Bu	Br	10:0	47
9	H	Me	*c*-C_6H_{11}	Br	7:3	50
10	H	Me	Ph	Br	—	—

[a] 30% corresponds to the isolated Prins product **5**.
[b] *anti*/*syn* ratio (3:7).

The process produced in moderate to good yield the unsaturated β-hydroxyketone **3**, with a range of aldehydes except when benzaldehyde was used (entries 4 and 10). Using 3-methylpent-4-yn-2-ol a *syn*/*anti* (3:7) unsaturated β-hydroxyketone, was obtained (entry 6). When cyclohexanal was used (entry 5), the Prins-tetrahydropyran **5** was the major product. The reaction is more selective with ferric bromide to the products **3** and **4** (entries 7 and 8), although with lower yields. Any attempt to control the final balance of the obtained products (**3**:**4**) under experimental conditions (temperature, addition order, solvent, etc.) proved to be fruitless.

In order to evaluate the factors in this domino process, we decided to study the influence of the substituents (R^1, R^2, R^3, and R^4) in the progress of the reaction (Table 2). It should be pointed out that although the propargylic portion (including the R^2 substituent) is lost[10] during the whole process it may influence the course of the reaction. Thus, we also evaluated the nature of the group R^2 and R^4. As indicated in Table 2, an aromatic substituent in both R^1 and R^2 are deleterious for the process, in R^2 yielding the α,β-unsaturated ketone, and R^1 impeding the reaction. Moreover when the alkyne is disubstituted (R^4 = Me, TIPS) the reaction is inhibited.

Table 2. Structure–reactivity relationship study of the addition of secondary homopropargylic alcohols and 3-methylbutanal using iron(III) chloride as promoter

Entry	R^1	R^2	R^4	**3**:**4**	Yield (%)
1	H	Me	H	7:3	65
2	H	*n*-C_2H_5	H	7:3	66
3	H	*c*-C_6H_{11}	H	7:3	61
4	H	Ph	H	0:10	87
5	H	4-BrPh	H	0:10	25
6	H	4-MePh	H	0:10	30
7	Ph	H	H	—	—
8	Ph	Ph	H	—	—
9	H	Me	TIPS	—	—
10	H	Me	Me	—	—
11	Me	Me	H	9:1	40

From this study, we have observed that the process depends basically on the nature of R^1, R^3, and R^4. We therefore decided to use commercially available pent-4-yn-2-ol and the suitable aldehyde as a possible 2,3-allenolate source. It should be pointed out that the nature of the aldehyde is a factor to consider, inasmuchas it can favor Prins reaction or the corresponding domino process (Table 1, entry 5).

The next step was the treatment of pent-4-yn-2-ol, in the presence of 3-methylbutanal, with various Lewis acids to evaluate the influence of the catalyst. The results are shown in Table 3.

When we use other Lewis acids such as $AlCl_3$ and $InCl_3$, similar results to $FeCl_3$ were obtained but the reactions were slower and the obtained yields lower. The methyl ketone **4** was the major product, when we use $BF_3{\cdot}OEt_2$ and iron(III) chloride combined with carboxylic or sulfonic acids (entries 7 and 8).[4b]

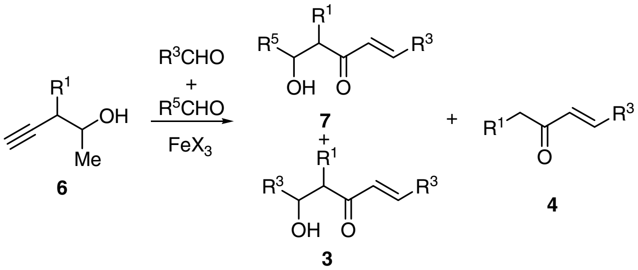
Using the optimized conditions, we pondered the possibility of running the reaction with two different aldehydes, taking advantage of different reactivities and attempting to obtain cross-over products.[11] The results of this study are summarized in Table 4.

In this experiment, a mixture of cross-over **7**, β-hydroxyketone **3** and α,β-unsaturated ketone **4** was obtained using iron(III) chloride as promoter (Table 4), product **7** being the major one (entries 1 and 2), except when an aromatic aldehyde with an electron-donating group was used (entry 3). When iron(III) bromide was used

Table 3. Addition of pent-4-yn-2-ol and 3-methylbutanal promoted by Lewis acids

Entry	Acids	Yield (%)	Ratio (**3**:**4**)
1	$AlCl_3$	47	6:4
2	$InCl_3$	54	7:3
3	$ZnCl_2$	—	—
4	$BF_3{\cdot}OEt_2$	75	0:10
5	$TiCl_4$	—	—
6	$CeCl_3$	—	—
7	$FeCl_3$/HOAc	65	2:8
8	$FeCl_3$/CSA	63	2:8

Table 4. Cross-over domino reaction of secondary homopropargylic alcohols and aldehydes using FeX_3 as catalyst

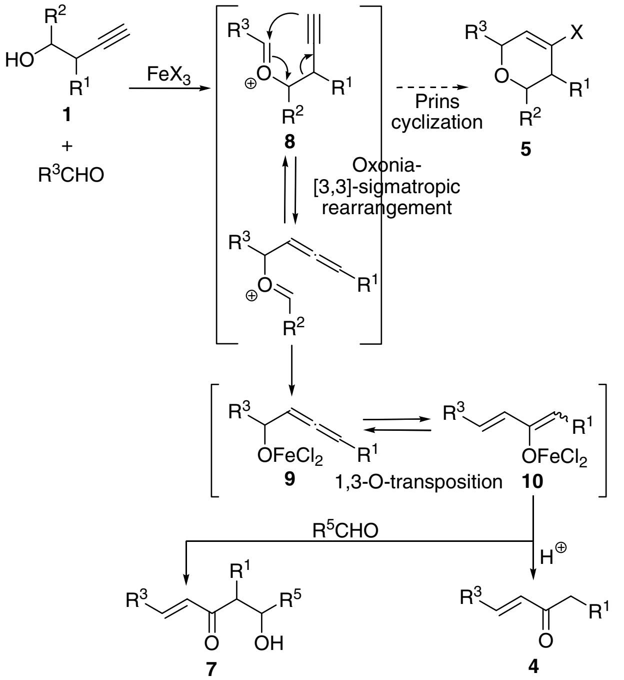


Entry	X	R^1	R^3	R^5	**7**:**3**:**4**	Yield (%)
1	Cl	H	*i*-Bu	*t*-Bu	5:3:2	47
2	Cl	H	*i*-Bu	C_6H_5	5:3:2	45
3	Cl	H	*i*-Bu	4-MePh	2:1:7	62
4	Br	H	*i*-Bu	C_6H_5	10:0:0	25
5	Br	Me	*i*-Bu	*t*-Bu	10:0:0	33[a]

[a] *anti*/*syn* ratio (1:1).

the process became completely chemoselective, the cross-over **7** being obtained as a single product, albeit with limited yield (entries 4–5). It must be emphasized that in this case aromatic aldehydes are valid substrates in the reaction.

A plausible mechanism for this new domino process is outlined in Scheme 4. The addition of homopropargylic alcohol and aldehyde promoted by ferric halide generates the oxonium ion **8** that undergoes an oxonium-[3,3]-sigmatropic rearrangement to give the allenolate **9**. Further intramolecular 1,3-oxygen transposition generates unsaturated enolate **10**.[5b] Subsequent coupling reaction with the suitable aldehyde or protonation conducts to compound **7** or **4**, respectively.



Scheme 4. Proposed mechanism for the addition of secondary propargylic alcohols and aldehydes.

The relative stability of the species involved on the oxonia [3,3]-sigmatropic rearrangement should address to an unsaturated β-hydroxyketone **7** or Prins-tetrahydropyran **5**. To evaluate the stability of these species 'ab initio' theoretical calculations at B3LYP/6-31G(d) level were performed (Table 5). A slight exothermic process was found for the studied models (entries 1–3). The bulkiness increment of R^3 (methyl to cyclohexyl) is concomitant with an increase in the activation energy of a transition state as shown in Figure 1. This fact is in agreement with the experimental data (Table 1, entry 5), where a Prins-tetrahydropyran was obtained as the major product.

To support 2,3-allenol[12] (**11**) as intermediate of this reaction, we performed a couple of runs using this substance as starting material and iron(III) chloride as catalyst (Scheme 5). We found the cross-over aldol (**12**) as the sole product when the reaction was run in the presence of the suitable aldehyde and the (*E*)-α,β-unsaturated ketone (**13**) in absence of the last one.

In conclusion, we report a novel oxonia [3,3]-sigmatropic rearrangement as competitive alternative pathway to the Prins cyclization, that leads to an allenol, further 1,3-*O*-transposition and enolate coupling. The address of the reaction (rearrangement or Prins type cyclization) depends directly on the stability of the species involved in the rearrangement, as shown by the 'ab initio' calculations, being favored this sigmatropic rearrangement. In this domino process, three consecutive chemical

Table 5. Ab initio calculations of the species involves on the 2-oxonia [3,3]-sigmatropic rearrangement

Entry	R^1	R^2	R^3	ΔH^* (kcal/mol)	ΔH (kcal/mol)
1	H	Me	Me	6.61	−3.24
2	H	Me	*i*-Pr	8.13	−0.69
3	H	Me	*c*-C_6H_{11}	10.02	−0.45

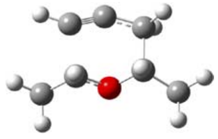
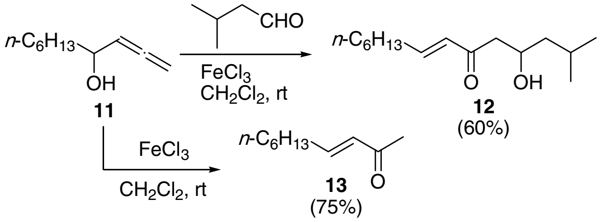


Figure 1. Transition state corresponding to entry 1 (Table 5).



Scheme 5. Coupling of 2,3-allenols and aldehydes catalyzed by iron(III) halides.

events take place in one-pot reaction (70–80% average). A noteworthy aspect of the reaction is that the carbon–carbon formation is very rapid and it is usually completed within 1 min. The reaction has been scaled up to 2 g with no difficulty.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.032.

References and notes

1. (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.
2. (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.
3. For recent advances in the Prins reaction, see: (a) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939–9945; (b) Rychnovsky, S. D.; Dalgard, J. E. *J. Am. Chem. Soc.* **2004**, *126*, 15662–15663, and references cited therein; (c) Dobbs, A. P.; Guesné, J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880–7883; (d) Yadav, V. K.; Kumar, N. V. *J. Am. Chem. Soc.* **2004**, *126*, 8652–8653; (e) Overman, L. E.; Velthuisen, E. J. *Org. Lett.* **2004**, *6*, 3853–3856; (f) Yu, C.-M.; Yoon, S. K.; Hong, Y. T.; Kim, J. *Chem. Commun.* **2004**, 1840–1841.
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.
5. (a) Trost, B. M.; Oi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1230–1231; (b) Trost, B. M.; Jonasson, C.; Wucher, M. *J. Am. Chem. Soc.* **2001**, *123*, 12736–12737.
6. Yu, C.-M.; Kim, Y.-M.; Kim, J.-M. *Synlett* **2003**, *10*, 1518–1520.
7. For a study describing the relatives rates of oxonia-Cope rearrangement versus Prins cyclization in the coupling of allylic alcohols and aldehydes, see Ref. 3a.
8. $FeCl_3$ and $FeBr_3$ were purchased form the Aldrich Chemical Co.
9. To the best of our knowledge, this is the first report on the use of Fe(III) halides promoting this kind of reaction.
10. We do not have any experimental evidence of the incorporation of this fragment in the course of the reaction.
11. *Typical experimental procedure for a ferric halide promoted domino reaction*: To a solution of homopropargylic alcohol (1 equiv) and aldehyde(s) (1 equiv of each) in dry CH_2Cl_2 was added anhydrous FeX_3 (1 equiv) in one portion. The reaction was concluded 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).
12. The allenic alcohol was prepared according to known procedures. Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943–7944.