Tetrahedron Letters, Vol.32, No.45, pp 6617-6620, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Stereo- and Regioselective Metal Salt-Catalyzed Alkynylation of 1,2-Epoxides

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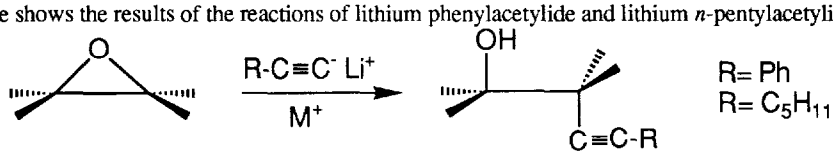
Abstract: *A simple, efficient, stereoselective, and highly regioselective method for the synthesis of β-hydroxyacetylenes by the direct opening of 1,2-epoxides with lithium acetylides in anhydrous THF, in the presence of metal salts, is described. This new method appears to be competitive and alternative to the other methods previously reported.*

β-Hydroxyacetylenes are useful in organic synthesis, particularly if one considers the versatility of the alkyne moiety in general,[1,2] and their application in prostaglandin[3a,b] and prostacyclin[3c] chemistry, in particular. The most common route to β-hydroxyacetylenes is the direct addition (displacement reaction) of metal acetylides to 1,2-epoxides: however, this reaction suffers from some intrinsic limitations, particularly when the substitution on the epoxide ring is increased, and the yields are usually not satisfactory.[1,4] Several modifications have been introduced into the original procedure in order to improve the results. For example, the use of lithium acetylides in aprotic polar solvent such as DMF[5a] or HMPA[5b] instead of Et_2O, the use of lithium acetylide·ethylendiamine complex in DMSO[6a] or HMPA,[6b,c] the presence of trimethylgallium as a catalyst,[6] or the use of alkynyl alanes[8] instead of the more usualy employed alkali-metal derivatives, generally lead to increased yields of the ring opened products. More recently, two new procedures have been suggested in order to effect the ring opening of epoxides with acetylides: the first one utilizes lithium acetylides in the presence of $BF_3{\cdot}Et_2O$,[9] and the second one utilizes titanium acetylides.[10] Yields are reported to be high for the former methodology,[9] and moderate to good for the latter one.[10] However, these techniques largely differ in the regiochemical result: whereas the ring opening of styrene oxide by lithium acetylide and $BF_3{\cdot}Et_2O$ affords mixtures of both the possible regioisomers,[9] the use of titanium derivatives leads only to the regioisomer arising from the attack of the nucleophile on the more substituted oxirane carbon.[10]

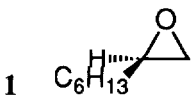
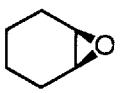
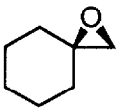
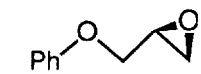
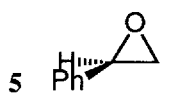
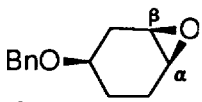
We recently discovered that common metal salts, such as $LiClO_4$, are able to catalyze in a very efficient way the direct aminolysis,[11a] azidolysis,[11b] and cyanidolysis[11c] of a large variety of oxiranes in aprotic solvents under very mild experimental conditions. These results prompted us to verify the possibility of transferring this type of catalysis also to the alkynylation of oxiranes.

It has been found that lithium acetylides in anhydrous THF react with 1,2-epoxides in the presence of metal salts: the Table shows the results of the reactions of lithium phenylacetylide and lithium *n*-pentylacetylide with



some representative 1,2-epoxides (**1-5**) in the presence of $LiClO_4$. For the sake of comparison, the Table shows the results of the reactions of the same epoxides **1-5** with the above-mentioned lithium acetylides carried out in the presence of $BF_3{\cdot}Et_2O$.[9] The reaction can be carried out also in the presence of other salts such as lithium

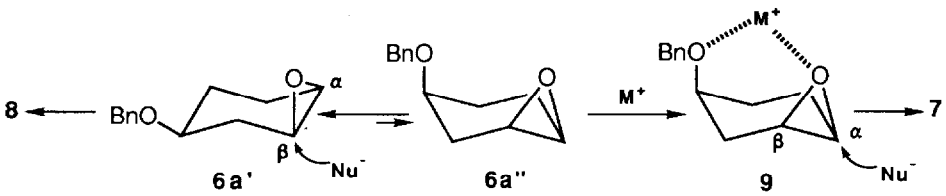
Table . Reaction of epoxides 1-6 with lithium acetylides, in anhydrous THF, in the presence of metal salts, and in the presence of $BF_3{\cdot}Et_2O$.[9]

entry	epoxide[a]	reagents and reaction conditions[b]		reaction time (h) and temperature	α attack[c]	β attack[d]	yield %[e]
1	 **1**	PhC≡CLi/ $LiClO_4$	A	24 (r.t.)	<1	>99*f*	96
2		PhC≡CLi/ BF_3*i*	B	0.5 (-78°C)	9*g*	91*f*	98
3		$C_5H_{11}C{\equiv}CLi$/ $LiClO_4$	A	24 (50°C)	<1	>99*h*	93
4		$C_5H_{11}C{\equiv}CLi$/ LiTf	A	24 (50°C)	<1	>99*h*	66
5		$C_5H_{11}C{\equiv}CLi$/ BF_3*i*	B	0.5 (-78°C)	11*g*	89*h*	95
6	 **2**	PhC≡CLi/ $LiClO_4$	A	72 (50°C)	*i,j*		80
7		PhC≡CLi	C	72 (50°C)	no reaction		
8		PhC≡CLi/ BF_3*i*	B	0.5 (-78°C)	*i,j*		100*i*
9		$C_5H_{11}C{\equiv}CLi$/ $LiClO_4$	A	72 (50°C)	*i,k*		80
10		$C_5H_{11}C{\equiv}CLi$	C	72 (50°C)	*i,k*		15
11		$C_5H_{11}C{\equiv}CLi$/ BF_3*i*	B	0.5 (-78°C)	*i,k*		93*i*
12	 **3**	PhC≡CLi/ $LiClO_4$	A	24 (r.t.)	<1	>99*l*	92
13		PhC≡CLi/ BF_3*i*	B	0.5 (-78°C)	<1	>99*l*	95
14		$C_5H_{11}C{\equiv}CLi$/ $LiClO_4$	A	24 (50°C)	<1	>99*m*	81
15		$C_5H_{11}C{\equiv}CLi$/ BF_3*i*	B	0.5 (-78°C)	<1	>99*m*	65
16	 **4**	PhC≡CLi/ $LiClO_4$	A	24 (r.t.)	<1	>99*n*	97
17		PhC≡CLi	C	24 (r.t.)	<1	>99*n*	22
18		PhC≡CLi/ BF_3*i*	B	0.5 (-78°C)	<1	>99*n*	97
19		$C_5H_{11}C{\equiv}CLi$/ $LiClO_4$	A	24 (r.t.)	<1	>99*o*	98
20		$C_5H_{11}C{\equiv}CLi$/ BF_3*i*	B	0.5 (-78°C)	<1	>99*o*	80
21	 **5**	PhC≡CLi/ $LiClO_4$	A	24 (r.t.)	6*g,p*	94*q*	96
22		PhC≡CLi/ $NaClO_4$	A	24 (r.t.)	2*g,p*	98*q*	38
23		PhC≡CLi	C	24 (r.t.)			2
24		PhC≡CLi/ BF_3*i*	B	0.5 (-78°C)	80*i,p*	20*i,q*	100*i*
25		$C_5H_{11}C{\equiv}CLi$/ $LiClO_4$	A	48 (50°C)	6*g,r*	94*s*	92
26		$C_5H_{11}C{\equiv}CLi$/ LiTf	A	48 (50°C)	10*g,r*	90*s*	97
27		$C_5H_{11}C{\equiv}CLi$	C	48 (50°C)	6*g,r*	94*s*	8
28		$C_5H_{11}C{\equiv}CLi$/ BF_3*i*	B	0.5 (-78°C)	50*i,r*	50*i,s*	79*i*
29	 **6**	PhC≡CLi/ $LiClO_4$	A	72 (r.t.)	68*t*	32*u*	90
30		PhC≡CLi/ BF_3*i*	B	0.5 (-78°C)	<1	>99*u*	95

[a] All the reactions were carried out on racemic material. [b] Tf= OSO_2CF_3; A, see General Procedure; B,see ref.9; C, as in A, no metal salt being added. [c] Attack of the nucleophile on the more substituted or, in the case of **6**, on the Cα oxirane carbon .[d] Attack of the nucleophile on the less substituted or, in the case of **6**, on the Cβ oxirane carbon. [e] Yields based on weight, GC analysis and ^{1}H NMR examination of the isolated crude reaction product. [f] Liquid, ^{1}H NMR δ 7.43-7.25 (m,5H), 3.82 (quintet,1H), 2.71-2.46 (m,2H). [g] Determined by ^{1}H NMR and GC. [h] Liquid,^{1}H NMR δ 3.68 (quintet,1H), 2.38-2.13 (m,4H). [i] see ref.9. [j] see ref.4d. [k] see ref.4b. [l] Solid,mp 46-47°C, ^{1}H NMR δ 7.45-7.25 (m,5H), 2.58 (s,2H). [m] Liquid,^{1}H NMR δ 2.32 (t,J=2.4 Hz,2H), 2.22-2.13 (m,2H). [n] Solid, mp 71-72°C ^{1}H NMR δ 7.43-6.92 (m,10H), 4.92-4.02 (m,3H), 2.81 (d,J=6.1 Hz,2H). [o] Liquid, ^{1}H NMR δ 7.34-6.89 (m,5H), 4.23-3.94 (m,3H), 2.55 (m,2H), 2.16 (m,2H). [p] See ref.10a. [q] Solid, mp 55-56.5°C,^{1}H NMR δ 7.50-7.20 (m,10H), 4.93 (t, J=6.3 Hz,1H), 2.85 (d, J=6.3 Hz,2H). [r] Liquid ^{1}H NMR δ 7.39-7.23 (m,5H), 3.86-3.75 (m,1H), 3.70-3.64 (m,2H), 2.25 (t, J=7.0 Hz,1H), 2.24 (t, J=7.0 Hz,1H). [s] Liquid,^{1}H NMR δ 7.40-7.22 (m,5H), 4.80 (dd, J=7.0 and 6.8 Hz,1H), 2.70-2.48 (m,2H), 2.29-2.11 (m,2H). [t] Compound **7**, mp 92-94 °C,^{1}H NMR δ 7.36-7.16 (m,10H), 4.51 (d, J=11.8 Hz,1H), 4.47 (d, J=11.8 Hz,1H), 3.74-3.56 (m,1H), 3.54-3.22 (m,1H), 2.67-2.58 (m,1H).[u] Compound **8**, liquid, ^{1}H NMR δ 7.42-7.22 (m,10H), 4.51 (s,2H), 3.70-3.56 (m,2H), 3.00-2.89 (m,1H).

triflate (entries 4 and 26, Table), while $NaClO_4$ turned out to be less effective (entry 22,Table) and $KClO_4$ and $Mg(ClO_4)_2$, not shown in the Table, not effective at all . The yields range from fair to good, and the reaction time and temperature from 24 h, room temperature or 50°C, for the more reactive epoxides, to 72 h and 50°C for the less reactive ones (see Table). When the reactions are carried out under the same experimental conditions but in the absence of any metal salt, the starting epoxides are recovered completely or almost completely unreacted (entries 7,10,17,23 Table). In the case of the more reactive epoxide **4** a certain amount of ring opened product was found, though this was less than 25%. The reactions are completely *anti* stereoselective as shown by the reactions of cyclohexene oxide (**2**) (entries 6 and 9, Table) where only the *trans* diastereisomer was found (GC and ^1H NMR). As for the regioselectivity of the nucleophilic addition on unsymmetrically substituted epoxides, the reactions are highly regioselective with the attack of the nucleophile on the less substituted oxirane carbon even in the case of styrene oxide (**5**) (entries 21,25, and 26, Table); in this case, the regiochemical result is consistently and interestingly different from what is observed in the reaction with titanium acetylides[10] and under $BF_3{\cdot}Et_2O$ catalysis.[9]

As previously discussed, [11] the catalytic ability of metal salts is a result of the coordination of the metal ion with the oxirane oxygen. Another interesting effect of the metal ion and particularly of Li^+ can be found in the following observation. The reaction of the *cis*-4-benzyloxy-1,2-epoxycyclohexane (**6**) (a homoallylic functionalized epoxide) with lithium phenylacetylide in the presence of $LiClO_4$ affords a 68:32 mixture of the two regioisomeric adducts **7** and **8**. When the same reaction is carried out without $LiClO_4$ and in the presence of $BF_3{\cdot}Et_2O$,only regioisomer **8** is obtained (entries 29 and 30,Table). This interesting result points to the previously



observed[12] chelating ability of Li^+ which makes epoxide **6** react, largely, in its less stable conformation (**6a"**) through the chelate structure **9**: the *trans* diaxial attack of the nucleophile (Nu^-) on **9** leads to compound **7**. On the other hand, $BF_3{\cdot}Et_2O$ is notoriously unable to give chelate structures:[13] as a consequence, epoxide **6** reacts in its more stable conformation (**6a'**) to give compound **8**, exclusively.

In conclusion, this new metal salt-catalyzed *anti*-stereoselective method for the cleavage of 1,2-epoxides by acetylides to give β-hydroxyacetylenes appears to be competitive compared with other procedures previously described.[4-10] The mild conditions, and the use of a mild Lewis acid makes this new method suitable for use with acid-sensitive substrates. Moreover, the high *contra*-Markovnikov[14] type regiochemistry observed makes this method advantageous in some cases with respect to the $BF_3{\cdot}Et_2O$ method,[9] and alternative to the titanium acetylide method.[10]

General Procedure and Identification of β-Hydroxyacetylenes

A solution of the alkyne (3.0 mmol) in anhydrous THF (5 ml) was treated under stirring at 0°C with 1.6 M BuLi in hexane (1.9 ml). After 10 min. at the same temperature, the reaction mixture was treated with a solution

of the epoxide (1.0 mmol) in anhydrous THF (2 ml) containing the anhydrous metal salt (2.0 mmol). The reaction mixture was then stirred for the time and at the temperature shown in the Table. Dilution with water, extraction with ether and evaporation of the washed (water) ether extracts afforded a crude reaction product which was analyzed by GC and ^{1}H NMR. β-Hydroxyacetylenes were identified by comparison (^{1}H NMR and GC) with authentic samples prepared in accordance with literature procedures.[4b,4d,9,10a] The structures of previously unreported β-hydroxyacetylenes (footnotes *f,h,l,m,n,o,q,r,s,t,u*, Table) were confirmed by satisfactory microanalysis results (C,H± 0.3% of the calculated value) and by their ^{1}H NMR spectra (200 MHz, see Table).

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14. The term "*contra*-Markovnikov" is preferred to "*anti*-Markovnikov" in order to avoid confusion with the stereochemical use of the prefix *anti*; see De La Mare P.B.D.; Bolton,R. *Electrophilic Additions to Unsaturated Systems*; Elsevier Scientific: Amsterdam, 1982.

Acknowledgment. *This work was supported by Consiglio Nazionale delle Ricerche (CNR) and Ministero della Universita' e della Ricerca Scientifica e Tecnologica (MURST), Roma.*

(Received in UK 5 September 1991)