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Synthesis of γ-Hydroxy Ketones by $LiClO_4$-Catalyzed Addition of Lithium Enolates to 1,2-Epoxides

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Key Words: γ-hydroxy ketones, epoxide opening reactions; regioselectivity; catalysts.

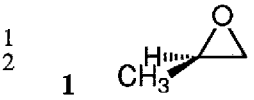
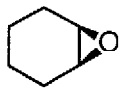
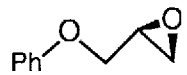
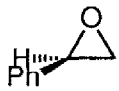
Abstract: *A simple, efficient, anti-stereoselective, highly regioselective method is described for the synthesis of γ-hydroxy ketones by the direct opening of 1,2-epoxides with lithium enolates derived from simple ketones in anhydrous THF, in the presence of $LiClO_4$.*

The construction of carbon-carbon bond constitutes one of the most important challenges in synthesis, particularly in the field of natural products.[1] The addition reaction of 1,2-epoxides are especially promising candidates for the development of new methods for carbon framework construction because of the large number of C-nucleophiles, beyond etheronucleophiles, which can be added and because they offer the potential of establishing multiple chiral centers per single skeletal elaboration step.[2] The addition reactions of metal alkyl and metal enolates derived from esters to 1,2-epoxides to give β-alkyl alcohols and γ-hydroxy esters, respectively, have been extensively studied.[2,3] Much less is known about the nucleophilic displacement of 1,2-epoxides with metal enolates derived from simple ketones. In an isolated report, Schreiber described the reaction of the lithium enolate of cyclononanone with propylene oxide in the presence of $AlMe_3$;[4] on the other hand, lithium enolate of 3-pentanone did not react with propylene oxide after 6 h at room temperature.[5] Dilithiooxime[6] and anionized Schiff base[7] of acetophenone react with 1,2-epoxides to yield γ-hydroxy ketones; however, in this case, hydrolysis of the intermediate oxime[6] or imine[7] is necessary in order to get free compound.

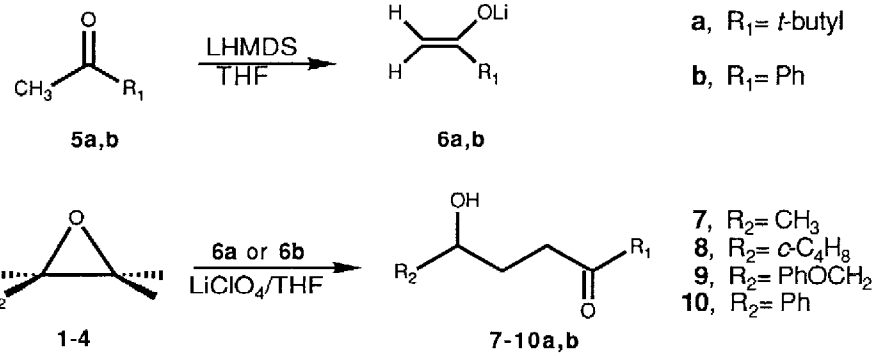
The discovery of the metal salt-catalyzed method for the ring opening of 1,2-epoxides with amines, azide and cyanide ion to give under mild conditions and in fair yields the corresponding opening products (amino alcohols, azido alcohols and β-hydroxy nitriles, respectively),[8] prompted us to verify if this new methodology could be successfully applied also to the direct nucleophilic displacement of 1,2-epoxides by lithium enolates of simple ketones.

We have found that the reaction of some representative epoxides (**1-4**) with lithium enolates (**6a** and **6b**) derived from pinacolone (**5a**) and acetophenone (**5b**), respectively, in the presence of $LiClO_4$ affords, in good to excellent yield, the corresponding γ-hydroxy ketones (**7-10 a,b**). The results obtained are summarized in the Table. Pinacolone and acetophenone, which generate enolate species possessing homotopic faces, were chosen in order to have no diastereoisomeric implications in the reaction with 1,2-epoxides under investigation; lithium enolates **6a** and **6b** were generated in anhydrous THF by means of lithium bis(trimethylsilyl)amide (LHMDS) (Aldrich): LHMDS was preferred to lithium diisopropylamide (LDA) and lithium 2,2,6,6-

Table. Reaction of epoxides 1-4 with enolates 6a and 6b, derived from pinacolone (5a) and acetophenone (5b), in THF in the presence of $LiClO_4$.

entry	epoxide[a]	enolate	reaction conditions,[b] time (h) and temperature		α attack[c]	β attack[d]	yield %[e]
1	 **1**	6a	A	72 h (25 °C)	<1	>99[f]	98
2		6b	A	72 h (25 °C)	<1	>99[g]	86
3	 **2**	6a	A	72 h (50 °C)		[h]	80
4		6a	B	72 h (50 °C)		[h]	17
5		6b	A	72 h (50 °C)		[i]	95
6		6b	B	72 h (50 °C)		[i]	12
7	 **3**	6a	A	24 h (25 °C)	<1	>99[j]	90
8		6a	B	24 h (25 °C)	<1	>99[j]	30
9		6b	A	24 h (50 °C)	<1	>99[k]	76
10		6b	B	24 h (50 °C)	<1	>99[k]	15
11	 **4**	6a	A	24 h (50 °C)	9[l]	91[m]	95
12		6a	B	24 h (50 °C)	9[l]	91[m]	30
13		6a	C	24 h (50 °C)	9[l]	91[m]	70
14		6a	D	24 h (50 °C)	8[l]	92[m]	30
15		6a	E	24 h (50 °C)	6[l]	94[m]	15
16		6b	A	24 h (50 °C)	12[n]	88[o]	80
17		6b	B	24 h (50 °C)	no reaction		

[a] Racemic material. [b] A: see General Procedure; B as in A, no $LiClO_4$ being added; C, as in A, an epoxide : enolate : $LiClO_4$=1: 1: 3 ratio being used; D, as in A, an epoxide : enolate : $LiClO_4$=1: 1: 2 ratio being used; E, as in B an epoxide : enolate=1 : 1 ratio being used. [c] Attack of the nucleophile on the more substituted oxirane carbon. [d] Attack of the nucleophile on the less substituted oxirane carbon. [e] Yields calculated on weight, GC and ^1H NMR analysis of the crude reaction product. [f] Compound **7a**. [g] Compound **7b**, see ref.6. [h] Compound **8a**. [i] Compound **8b**. [j] Compound **9a**. [k] Compound **9b**. [l] Determined by ^1H NMR and GC. [m] Compound **10a**. [n] Compound **11b**. [o] Compound **10b**, see ref.7.



tetramethylpiperidide (LTMP) because of the lack of implications due to competitive aminolysis by the free amine (hexamethyldisilazane) on 1,2-epoxides under metal salt catalysis,[8a] as sometimes observed with diisopropylamine and 2,2,6,6-tetramethylpiperidine derived from LDA and LTMP, respectively.[9] Reaction times and temperatures range from 24 h, at 25 °C for the more reactive epoxide **3** to 72 h at 50 °C for the less reactive epoxide **2**. The catalytic efficiency of $LiClO_4$ as the ability of Li^+ to coordinate to the oxirane oxygen[8] is demonstrated by some control reactions carried out in the same experimental conditions, but in the absence of the metal salt (entries 4,6,8,10,12,and 17,Table). In these reactions the starting epoxides were found completely unreacted or only partially reacted (about or less than 30%). An epoxide : enolate : $LiClO_4$=1: 2.5 : 1.5 molar ratio is commonly used (see General Procedure); however, almost the same experimental result can be obtained with an epoxide : enolate=1 : 1 molar ratio, if a threefold excess of $LiClO_4$ is contemporarily used (entry 13, Table). The reactions are completely *anti* stereoselective, no *syn* adduct being detected in the reaction carried out on epoxide **2**. When unsymmetrical epoxides are considered, the reaction is highly regioselective with the attack of the nucleophile (enolate ion) on the less substituted oxirane carbon to give the *contra*-Markovnikov[10] type adduct.

In conclusion, the method here described appears to be a valuable tool for chemists for the synthesis of γ-hydroxy ketones, in particular, and, in general, for the construction of more complex di- or multifunctionalized compounds deriving from them.

General Procedure and Identification of the γ-Hydroxy Ketones

A 1.0 M LHMDS solution in THF (6.0 ml) (Aldrich) was treated under stirring at 0°C with a solution of the ketone (5.0 mmol) in anhydrous THF (1 ml), added in about 15 min. After 30 min at the same temperature, a solution of the epoxide (2.0 mmol) in anhydrous THF (2 ml), containing anhydrous $LiClO_4$ (3.0 mmol) was added in 10 min, and the resulting reaction mixture was 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 ^1H NMR. Preparative TLC afforded pure γ-hydroxy ketones which were identified on the basis of their ^1H and ^{13}C NMR spectra and confirmed by satisfactory microanalysis results (C,H $\pm$ 0.3% of the calculated value).

Compound **7a** : liquid; ^1H NMR δ 3.69-3.84 (m,1H), 2.65 (t,2H, J=7.1 Hz), 1.54-1.83 (m,2H), 1.19 (d,2H, J=6.1 Hz), 1.15 (s,9H). ^{13}C NMR δ 217.51, 67.78, 44.71, 33.43, 26.96, 24.14.

Compound **7b** :[6] liquid; ^1H NMR δ 7.93-8.01 (m,2H), 7.39-7.67 (m,3H), 3.70-3.95 (m,1H), 3.13 (t,2H, J=6.9 Hz), 1.70-2.01 (m,2H), 1.22 (d,3H, J=6.2 Hz). ^{13}C NMR δ 201.38, 133.65, 129.14, 128.92, 128.67, 67.80, 35.50, 33.68, 24.30.

Compound **8a**: solid, mp 46-47°C; ^1H NMR δ 3.14 (m,1H), 2.80 (dd,1H, J=17.5 and 5.5 Hz), 2.43 (dd,1H, J=17.5 and 6.1 Hz), 1.14 (s,9H). ^{13}C NMR δ 218.04, 75.85, 44.95, 41.76, 41.70, 36.82, 32.64, 26.98, 26.18, 25.64.

Compound **8b**: solid, mp 81-82°C; ^1H NMR δ 7.95-8.01 (m,2H), 7.27-7.60 (m,3H), 3.43 (dd,1H, J=16.4 and 5.2 Hz), 3.26 (m,1H), 2.79 (dd,1H, J=16.4 and 6.9 Hz). ^{13}C NMR δ 202.05, 137.80, 133.63, 129.15, 128.87, 75.69, 43.46, 42.53, 36.72, 32.47, 26.12, 25.58.

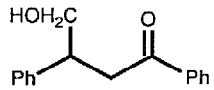
Compound **9a**: solid, mp 37-38°C; ^{1}H NMR δ 7.24-7.34 (m,2H), 6.87-7.00 (m,3H), 3.80-3.89 (m,3H), 2.68-2.80 (m,2H), 1.67-1.96 (m,3H), 1.17 (s,9H) . ^{13}C NMR δ 217.15, 159.15, 130.17, 121.75, 115.17, 76.66, 70.23, 44.86, 33.33, 27.72, 27.14.

Compound **9b**: solid, mp 111-113°C; ^{1}H NMR δ 7.98-8.02 (m,2H), 7.26-7.61 (m,5H), 6.89-7.01 (m,3H) 3.87-4.16 (m,3H), 3.26 (t,2H, J=7.0 Hz), 1.88-2.14 (m,2H). ^{13}C NMR δ 200.00, 159.15, 137.47, 133.87, 130.21, 129.31, 128.77, 121.84, 115.23, 72.86, 72.66, 70.26, 35.28, 27.93.

Compound **10a**: liquid; ^{1}H NMR δ 7.16-7.36 (m,5H), 4.66 (dd,1H, J=5.4 Hz), 2.59 (t,1H, J=7.3 Hz), 2.58 (t,1H, J=6.5 Hz), 1.91-2.02 (m,2H), 1.10 (s,9H). ^{13}C NMR δ 217.42, 145.11, 128.95, 127.90, 126.31, 73.98, 44.75, 33.42, 27.05.

Compound **10b**:[7] solid, mp 95.5-96°C (lit.[7] mp 96°C); ^{1}H NMR δ 7.81-7.96 (m,2H), 7.26-7.59 (m,8H), 4.82 (dd,1H, J=5.7 Hz), 3.11 (t,2H, J=7.0 Hz), 2.14-2.25 (m,2H). ^{13}C NMR δ 200.55, 144.29, 136.74, 133.11, 128.54, 128.47, 128.06, 127.54, 125.71, 73.55, 34.73, 33.01.

Compound **11b**: solid, mp 98-99°C; ^{1}H NMR δ 7.92-7.97 (m,2H), 7.23-7.56 (m,8H), 3.83 (m,2H), 3.55-3.67 (m,1H), 3.30-3.47 (m,2H). ^{13}C NMR δ 207.79, 141.77, 133.18, 128.78, 128.59, 128.13, 127.83, 127.00, 67.07, 43.39, 41.44.



11b

References and notes

1. Corey,E.J.; Cheng,X-M. *The Logic of Chemical Synthesis* John Wiley, New York, 1989.
2. Gorzynski Smith,J. *Synthesis* **1984**, 629-656.
3. Flippin,L.A.; Brown,P.A.; Jalali-Araghi,K. *J.Org.Chem.* **1989**, *54*, 3588-3596 and references therein.
4. Schreiber,S.L. *J.Am.Chem.Soc.* **1980**, *102*, 6163-6165.
5. Sturm,T-J.; Marolowski,A.E.; Rezenka,D.S.; Taylor,S.K. *J.Org.Chem.* **1989**, *54*, 2039-2040.
6. Bellassoued,M.; Dardoize,F.; Gaudemar,M. *J.Organomet.Chem.* **1979**, *177*, 35-38.
7. Wittig,G.; Fischer,S.; Tanaka,M. *Justus Liebigs Ann.Chem.* **1973**, 1075-1081.
8. a) Chini,M.; Crotti,P.; Macchia,F. *Tetrahedron Lett.* **1990**, *31*, 4661-4664. b) 5641-5644. c) Chini,M.; Crotti,P.; Favero,L.; Macchia,F. *ibid.* in press.
9. Unpublished results from our laboratory.
10. 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.

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