Synthesis of γ-Lactones by Nucleophilic Addition of Carboxylic Acid Enediolates to Epoxides.

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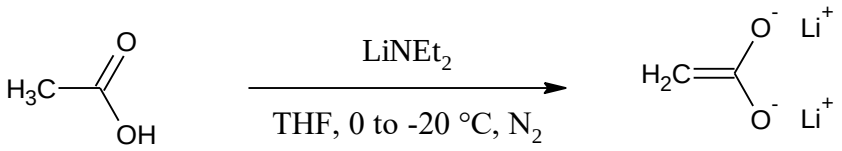
Abstract: We have reported the nucleophilic attack of carboxylic acid enediolates to epoxides to form γ-lactones resulting from attack at less substituted carbon atom of epoxide. We have used lithium dialkylamides for the generation of dianions of carboxylic acid. The reaction works efficiently with epoxides and forms γ-lactones at higher yield under nitrogen atmosphere.

Keywords: Lactones, lithium chloride, carboxylic acid, epoxide, Nucleophilic addition, enediolate.

Introduction: The epoxide ring opening by nucleophiles is a frequently required transformation for the synthesis of organic compounds[1], usually in the formation of lactones.[2] Addition of the enediolates of carboxylic acids to epoxides reported a few years ago with irregular results.[3] Enolates as carbon based nucleophiles for organic synthesis , typical lithium enolates of esters and ketones do not react directly with epoxides. The usefulness of epoxides in S_N2 reactions has been studied and important limitations precisely due to its key mechanistic aspect have been detected.[4] The use of sub-stoichiometric amount of amine for the dianion generation permits minimization of other nucleophiles present in the reaction medium, thus avoiding the generation of amino alcohols.[5] Carboxylic acid enediolates undergo reactions with epoxides to give lactones.[6] The reaction display the typical characteristic of S_N2 substitution, including preferential substitution at the less substituted epoxide carbon.[7] The reactions of epoxides and carbanion nucleophiles are very important transformations in the synthesis of biologically important targets.[8-10] one of the most important of these reactions is the reactions of enolates of ketones and esters with epoxides.[11-12] The γ-lactone is key structural motif in many natural products, most notably the sesquiterpene lactone.[13] γ-Lactones are very important moieties in natural products, products of biological importance, perfumes, and food additives.[14-16] Thus, many synthetic approaches for the synthesis of lactones have been devised, utilizing as starting materials carboxylic acids.[17-20.] Five membered lactone (γ-lactone) containing natural products are known to exhibit various biological activities such as cytotoxic,[21] antitumor,[22] cyclooxygenase or phospholipase A2 inhibition.[23] γ-Lactones have attracted much attention in organic and medicinal chemistry due to the extensive occurrence in numerous biologically active natural products,[24-28] and also versatile utility as synthetic intermediates in the synthesis of a wide range of bioactive compounds.[29-32] Therefore, a number of new synthetic route for γ-lactones have been reported in recent years.[33-38]

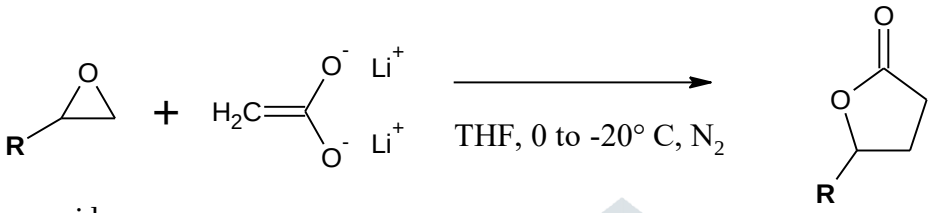
Experimental: i) Preparation of enediolate : carboxylic acid (1 mol) in dry THF were slowly added to the stirred lithium amide (2 mol) at 0 ° c and cooled again to -20 ° c for 30 minutes.

ii) Preparation of γ-lactone : The solution of epoxide (1 mol) in THF were added dropwise by gas tight syringe to the dianion solution at 0 ° c (1 mol) and temperature of the solution maintained at -20° c for 30 min. the reaction mixture quenched with water and mixture extracted with diethylether , the aqueous layer acidified with conc. HCl and extracted with ethylacetate (03x 10 ml). and dried over magnesium sulphate. The crude lactone obtained purified by coloumn chromatography.



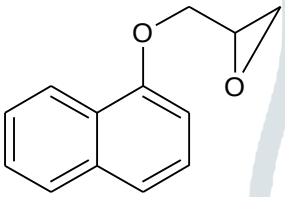
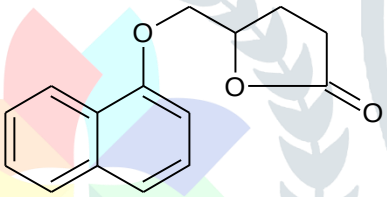
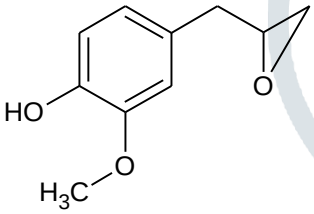
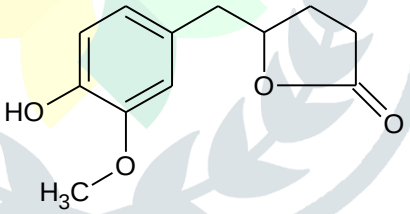
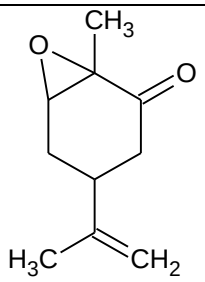
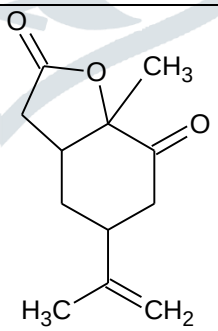
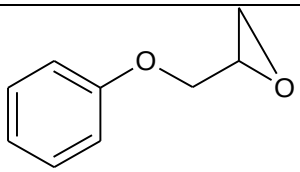
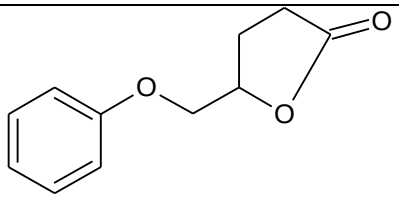
acetic acid enediolate

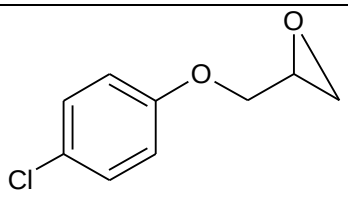
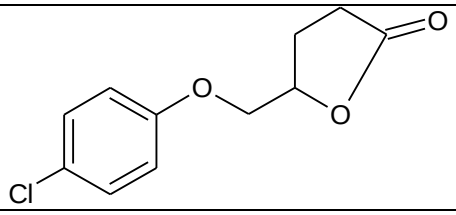
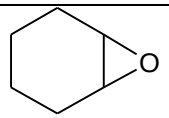
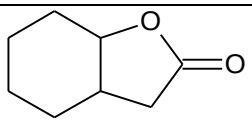
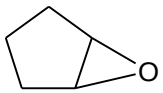
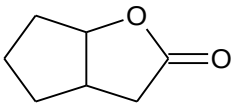
Reaction scheme: Generation of enediolate from acetic acid and lithium amide.



epoxide lactone

Reaction scheme: Synthesis of lactone from epoxide.

Reactant	Product	Time (Min)	Yield (%)
		35	76
		40	72
		52	69
		30	78

		65	70
		35	74
		28	65

Results and discussion: In the present study, the lactones were synthesized by the action of carboxylic acid enediolates with various epoxides. We have observed that the different results obtained when dianion of acetic acid reacts with various epoxides given in the above table. The progress of the reactions monitored by using thin layer chromatography. Products synthesized were characterized by spectroscopic techniques like I. R and NMR. Yields are high, neucleophilic dianion reagent is homogeneous solution and stable at 0° c. The products γ-lactones synthesized shows various biological activities like Cardiovascular analeptic, phosphatase inhibitor, phobic disorders treatment, antineoplastic and respiratory analeptic checked by using PASS (prediction of activity spectra for substances) online software.

Conclusion: We have developed a new approach to the synthesis of γ-lactones by nucleophilic addition of carboxylic acid enediolates to the various epoxides. The study of nucleophilic substitution reactions shows that it is highly regioselective. it shows that the incoming nucleophile reacts at less substituted carbon atom of epoxide. With this research work, it could be possible to synthesize compounds which are biologically active. It has been observed that the sterically hindered epoxide requires more reaction time for the complete conversion of reaction to products.

References:

1) Tylor S. K. **2000.** Reactions of Epoxides with Ester, Ketone and Amide Enolates. *Tetrahedron*, *56*, 1149-1163.

2) P. L. Creger, **1972**, Reactions of metalated carboxylic acids with epoxides, *J. Org Chem*. *37*, 1907-1918.

3) A. G. Myres, L. McKistry, **1996**, Practical Syntheses of Enantiomerically Enriched γ-Lactones and γ-Hydroxy Ketones by the Alkylation of Pseudoephedrine Amides with Epoxides and Their Derivatives, *J. Org. Chem.*, *61*, 2428-2440.

4) Izquierdo, J,; Lopez, I,; Rodriguez, S,; Gonzalez, F. **2006**, Epoxides as useful synthetic building blocks, *Recent Res. Devel. Org. Chem. 10*,53-61.

5) Gil, S.; Torres, M,; Ortuzar, N,; Wincewick, R,; Parra, M,; **2004**, Efficient addition of acid enediolates to epoxie, *Eur. J. Org. Chem.*, 2160-2165.

6) Petragnani, N,; Yonashiro, M,; **1982**, The Reactions of Dianions of Carboxylic Acids and Ester Enolates, *Synthesis*, 521.

7) Danishefsky, S,; Tsai, M-Y,; Kitahara, T,; **1977**, Specific directing effects in the opening of vicinal hydroxy epoxides, *J. Org. Chem*., *42*, 394

8) Schneider, C. **2006**, Synthesis of 1,2-difunctionalized fine chemicals through catalytic, enantioselective ring-opening reactions of epoxides. *Synthesis*, 3919–3944.

9) Pineschi, M. **2006**, Asymmetric ring-opening of epoxides and aziridines with carbon nucleophiles. *Eur. J. Org. Chem.*, 4979–4988.

10) Taylor, S.K. **2000**, Reactions of epoxides with ester, ketone and amide enolates. *Tetrahedron*, 56, 1149–1163.

11) Sturm, T.J.; Marolewski, A.E.; Rezenka, D.S.; Taylor, S.K. **1989**, Diastereoselective reactions of ester enolates with epoxides. *J. Org. Chem*., 54, 2039–2040.

12) Yura, T.; Iwasawa, N.; Clark, R.; Mukaiyama, T. **1986**, Asymmetric sulfenylation of tin (ii) enolates of ketones and 3-acyl-2-oxazolidones. Application to the synthesis of optically active epoxides. *Chem. Lett*., 15,
1809–1812.

13) Hoffmann H. M. R,; Rabe, **1985,** *J. Angew. Chem. Int. Ed. Engl*., Synthesis and Biological Activity of a-Methylene-y-butyrolactones, *24*, 94-110.

14) Pertino, M. W.; Theoduloz, C.; Rodriguez, J. A.; Yanez, T.; Lazo, V.; Schmeda-Hirschmann, G. **2010,** Gastroprotective Effect of Carnosic Acid γ-Lactone Derivatives**,** *J. Nat. Prod*., 73, 639.

15) Cooke, R. C.; Capone, D. L.; van Leeuwen, K. A.; Elsey, G. M.; Sefton, M. A. J. Agric. **2009**, *Food Chem*., 57, 348.

16) Jogi, A.; Paju, A.; nPehk, T.; Kailas, T.; Muurisepp, A.-M.; Lopp, M. **2009**, Synthesis of 4′-aryl-2′,3′-dideoxynucleoside analogues, *Tetrahedron*, 65, 2959.

17) Dohi, T.; Takenaga, N.; Goto, A.; Maruyama, A.; Kita, Y. **2007**, Direct Lactone Formation by Using Hypervalent Iodine(III) Reagents with KBr via Selective C−H Abstraction Protocol, *Org. Lett*., 9, 3129.

18) Gooβen, L. J.; Ohlmann, D. M.; Dierker, M. **2010**, Silver triflate-catalysed synthesis of γ-lactones from fatty acids, *Green Chem*., 12, 197.

19) Li, J.; Yang, S.; Jiang, H.; Wu, W.; Zhao, J. **2013**, Palladium-Catalyzed Coupling of Alkynes with Unactivated Alkenes in Ionic Liquids: A Regio- and Stereoselective Synthesis of Functionalized 1,6-Dienes and Their Analogues, *J. Org. Chem.*, 78, 12477.

20) Triandafillidi, I.; Raftopoulou, M.; Savvidou, A.; Kokotos, C. G. **2017**, Organocatalytic Synthesis of Lactones by the Oxidation of Alkenoic Acids, *Chem. Cat. Chem* , *9* ,4120.

21) Li, D. H.; Zhu, T. J.; Liu, H. B.; Fang, C. Y.; Gu, Q. Q.; Zhu, W. M. Arch. **2006**, *Pharm. Res*., *29*, 624.

22) . Cateni, F.; Zilic, J.; Zacchigna, M.; Bonivento, P.; Frausin, F.; Scarcia, V. **2006**, Synthesis and biological properties of new α-methylene-γ-butyrolactones and α,β-unsaturated δ-lactones, *Eur. J.Med. Chem*., *41*, 192.

23) Ma, S.; Shi, Z.; Yu, Z. **1999**, *Tetrahedron*, Synthesis of β-halobutenolides and their Pd(0)-catalyzed cross-coupling reactions with terminal alkynes and organozinc reagents. A general route to β-substituted butenolides and formal synthesis of cis-whisky lactone, *55*, 12137.

24) Koch, S. S. C.; Chamberlin, A. R. In Studies in Natural Products Chemistry; Atta-ur-Rahman, **1995**, *Ed.; Elsevier*: Amsterdam,; *16*, 687–725.

25) Rao, Y. S. **1976**, Recent advances in the chemistry of unsaturated lactones, *Chem. Rev*., 76, 625.

26) Mulzer, J.; Salimi, N.; Hartl, H. **1993**, *Tetrahedron: Asymmetry*, *4*, 457.

27) Schmitz, W. D.; Messerschmidt, N. B.; Romo, D. **1998**, A β-Lactone-Based Strategy Applied to the Total Synthesis of (8S,21S,22S,23R)- and (8R,21S,22S,23R)-Okinonellin B, *J. Org. Chem*., *63*, 2058;

28) Maier, M. S.; Marimon, D. I. G.; Stortz, C. A.; Adler, M. J. **1999**, A Revised Structure for (−)-Dihydropertusaric Acid, a γ-Butyrolactone Acid from the Lichen Punctelia microsticta, *J. Nat. Prod*., *62*, 1565.

29) Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, **1998**, *E. J. Org. Chem*., *63*, 2385.

30) de March, P.; Figueredo, M.; Font, J.; **2000**, Raya, Highly Efficient, Enantioselective Synthesis of (+)-Grandisol from a C2-Symmetric Bis(α,β-butenolide), *J. Org. Lett*. *2*, 163.

31) He, M.; Lei, A.; Zhang, X. **2005**, *Tetrahedron Lett*., *46*, 1823;

32) Delhaye, L.; Merschaert, A.; Diker, K.; Houpis, I. N. **2006**, Synthesis of 4,4′-Disubstituted Azepines via Ring-Closing Metathesis Reaction and Asymmetric Arylation of Lactones, *Synthesis*, 1437.

33) (a) Gutierrez, J. L. G.; Jimenez-Cruz, F.; Espinosa, N. R. **2005**, *Tetrahedron Lett*., *46*, 803.

34) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. **2006**, *Synthesis*, N-Heterocyclic Carbene-Catalyzed Conjugate Umpolung for the Synthesis of γ-Butyrolactones, 2418.

35) Tiecco, M.; Testaferri, L.; Temperini, A.; Terlizzi, R.; Bagnoli, L.; Marini, F.; Santi, C. **2006**, Synthesis of γ- and δ-Lactones from Alkynols, *Synlett*, 587.

36) Vitale, M.; Prestat, G.; Lopes, D.; Madec, D.; Poli, G. **2006**, *Synlett*, A Palladium-Catalyzed Sequence of Allylic Alkylation and Hiyama Cross-Coupling: Convenient Synthesis of 4-(α-Styryl) γ-Lactones, 2231.

37) Cho, C. S.; Shim, H. S. **2006**, *Tetrahedron Lett*., *47*, 3835;

38) Dias, L. C.; de Castro, I. B. D.; Steil, L. J.; Augusto, T. **2006**, *Tetrahedron Lett*., *47*, 213.