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# DIANION OF 1,2-BIS(4',4'-DIMETHYL-2'-OXAZOLIN-2'-YL)ETHANE VERSATILE SYNTHETIC REAGENT FOR ANNULATION

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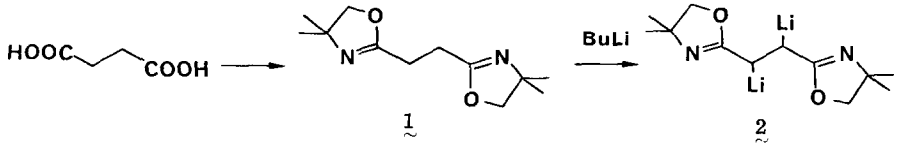
Summary: Treatment of 1,2-bis(4',4'-dimethyl-2'-oxazolin-2'-yl)ethane with butyllithium produced the corresponding dianion, which on exposure with 1, ω -dihalides gives cyclic derivatives. The same dianion reacts with the β-bromoesters to yield substituted cyclopentanones.

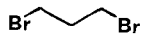
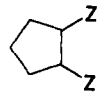
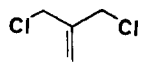
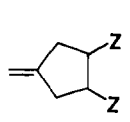
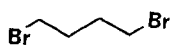
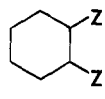
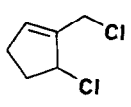
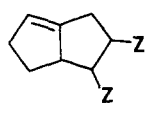
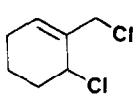
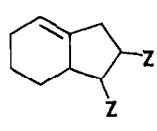
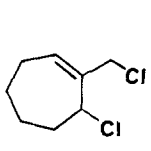
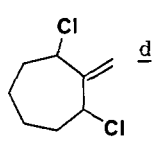
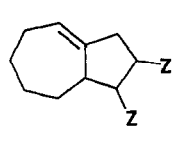
The analysis of a synthetic problem to produce a plan of synthesis of complex cyclic molecules usually depends more heavily on the processes available for ring formation than on any other class of synthetic operation. Accordingly, the addition of new methods in this area is of particular importance. In the preceding papers,[1,2] we have described a synthesis of substituted cyclopentanones from the dianion of dialkyl succinate and β-bromopropionates. In addition the versatility of such process was demonstrated by conversion to prostaglandins and sarkomycines. In continuation of our research on new annulation methods we next turned to the exploitation of the reactions of dianions of 2-oxazolines.[3] Such dianions appeared deserving of study since the dilithio derivatives are available simply and in high yield, and their chemical reactivities seemed appropriate. We now describe several key reactions of oxazoline based dianions which form a basis for a broad range of synthetic applications.

1,2-Bis(4',4'-dimethyl-2'-oxazolin-2'-yl)ethane (1) was previously unknown, but its preparation was accomplished simply by heating a mixture of succinic acid and 2-amino-2-methyl-1-propanol (1:2) in xylene at reflux for 10 h (60~70%).[4] Metallation of the crystalline oxazoline 1 was effected cleanly by 2 molar equiv of n-butyllithium in tetrahydrofuran at -78°C for 30 min. The dilithio derivative 2 thus obtained reacted with 1 equiv of dihalide at -78°C for 1 h and 20°C for 1 h, giving the corresponding




1 2

Table I. Reaction of Dilithiated Oxazoline 2 with Dihalides [a]

| Entry | Dihalide [5] | Product [b] | Yield (%) [c] |
|---|---|---|---|
| 1 |  |  | 69 |
| 2 |  |  | 68 |
| 3 |  |  [6] | 69 |
| 4 |  |  | 78 |
| 5 |  |  | 51 |
| 6 |  |  | 74 |
| 7 |   [d] |  | 83 |

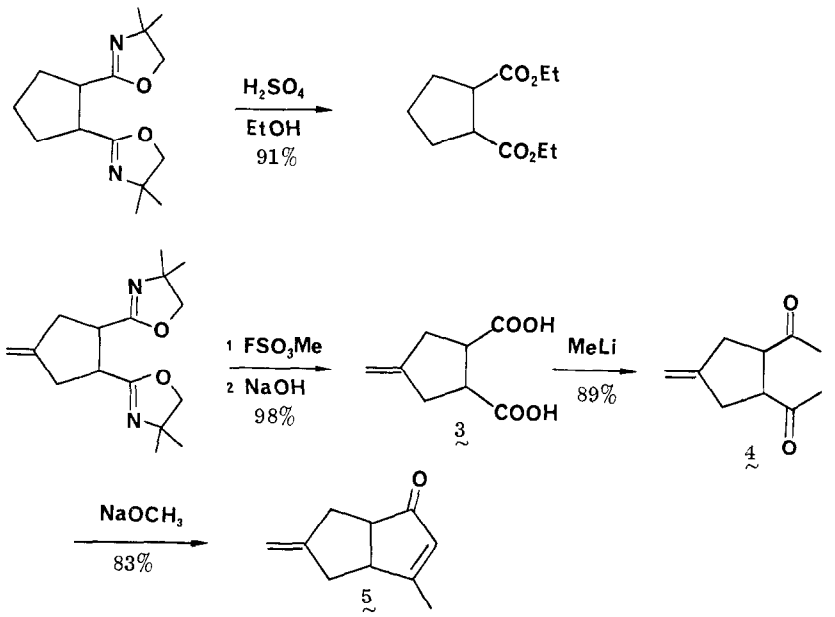
[a] All reactions were carried out in THF under $N_2$ atmosphere at -78°C for 1 h, and then at 20°C for 1 h.

[b] All products have been characterized by spectral data. Z = 4,4-dimethyl-2-oxazolin-2-yl

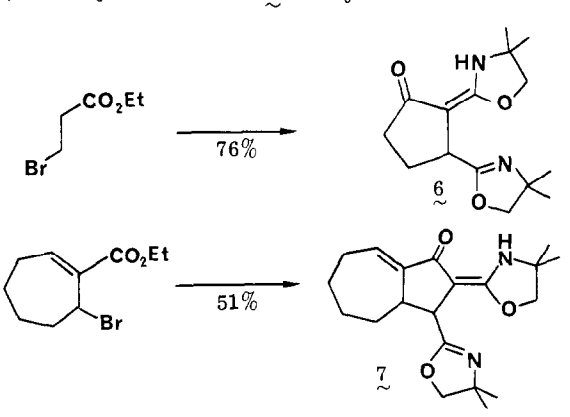
[c] Isolated yield after silica gel column chromatography.

[d] Mixture of two regio-isomers.

cyclic compounds in synthetically acceptable yields. Table I summarizes some of the results obtained with 2 using a wide variety of dihalides.[5] Acid hydrolysis of the resulting cyclic derivatives affords the dicarboxylic acids, whereas alcoholysis provides the corresponding diesters in high yields.[3] The dicarboxylic acid 3 may be further converted to the diketone 4 on exposure with methyllithium at low temperature.[7] Cyclization of 4 was effected by treatment with sodium methoxide in methanol to give the bicyclic structure 5 in 83% yield.[8]




In order to prove further the generality and limitations of the bis-oxazoline dianion chemistry, we turn our attention to the possibility of synthesizing cyclopentanone directly from β-bromoesters.[2] Ethyl 3-bromopropionate, when treated with the anion 2 at -78°C, gave exclusively the product of cyclopentanone 6.[9] Further, the bicyclic structure 7 was synthesized under the similar conditions.[10]



References and Notes

1. K. Furuta, A. Misumi, A. Mori, N. Ikeda, H. Yamamoto, Tetrahedron Lett., preceding paper.

2. A. Misumi, K. Furuta, H. Yamamoto, Tetrahedron Lett., preceding paper.

3. For the alkylation using lithio salt of 2,4,4-trimethyl-2-oxazoline, A. I. Meyers, D. L. Temple, R. L. Nolen, E. D. Mihelich, J. Org. Chem., 39, 2778 (1974) and references therein.

4. $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (s, 12 H), 2.57 (s, 4H), 3.90 (s, 4H).

5. 1-Chloromethyl-5-chlorocyclopentene was prepared from ethyl 5-hydroxycyclopentenecarboxylate in 3 steps: (1) protection of hydroxy group (t-Bu$Me_2$SiCl, imidazole, DMF, 95%); (2) reduction (DIBAH) and desilylation ($Bu_4NF$) (93%); (3) chlorination ($PCl_3$, 81%). Six- and seven-membered ring analogues were prepared by direct chlorination of olefins with t-butyl hypochlorite: see, W. Sato, N. Ikeda, H. Yamamoto, Chem. Lett., 141 (1982).

6. Product of entry 3: $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (s, 12H), 2.4-3.3 (m, 6H), 3.90 (s, 4H), 4.90 (m, 2H); IR ($CCl_4$) 1670 cm$^{-1}$.

7. M. J. Jorgenson, Org. React., 18, 1 (1970).

8. $^1$H NMR ($CDCl_3$) $\delta$ 2.1 (s, 3H), 2.17-3.4 (m, 6H), 4.77 (br. s, 2H), 5.83 (br. s, 1H); IR ($CCl_4$) 1710 cm$^{-1}$.

9. $^1$H NMR ($CDCl_3$) $\delta$ 1.25, 1.4 (2s, 12H), 1.83-2.6 (m, 4H), 3.5-4 (m, 1H), 3.87, 4.1 (2s, 4H), 6.27 (br. s, 1H).

10. $^1$H NMR ($CDCl_3$) $\delta$ 0.83-2.9 (br. m, 21H), 3.32 (d, 5 Hz, 1H), 3.67-4.17 (m, 4H), 6.5 (br. s, 1H), 7.17 (br. s, 1H); IR ($CCl_4$) 1650, 1560 cm$^{-1}$.

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