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AN IMPORTANT ROLE PLAYED BY DIANIONES IN THE HIGHLY EFFICIENT MACROCYCLE FORMATION BY AN INTRAMOLECULAR ALKYLATION METHOD: APPLICATION TO THE SYNTHESIS OF ZEARALENONE

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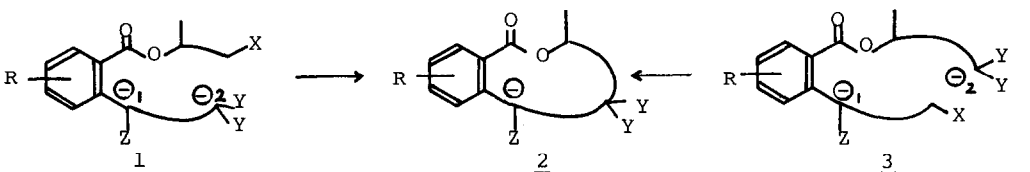
Summary: A new synthetic method for macrolides based on intramolecular alkylation of dianions, generated from phenylthiomethyl group and protected cyanohydrin, is reported. The use of dianions for the cyclization has several characteristic features; (1) Control of the conformation of the side-chain, (2) Protection of the ester from a nucleophilic attack, (3) Acceleration of the intramolecular reaction without using high dilution conditions. To prove these speculations, the alkylation using the dianions 5 and 6 was examined in the synthesis of zearalenone.

Synthesis of naturally occurring macrocyclic compounds is one of the fields of active study in organic chemistry.[1] In this connection, discovery of efficient cyclization methods of macrocycles constitutes the key feature of the research. The good cyclization method should be very rapid and irreversible, and afford high yields of cyclized products. Also tedious high dilution technique should be avoided from a practical standpoint. In our continuous effort to explore cyclization methods based on carbon-carbon bond formation, we have introduced the ring formation by intramolecular alkylation of anions generated from phenylthiomethyl group[2] and protected cyanohydrins.[3] We have synthesized several macrolides and macrocyclic ketones in high yields by these alkylation methods. In this paper we wish to report further improvement of the cyclization method for the syntheses of orsellinic acid type macrolides.

In this method the following dianions are subjected to intramolecular alkylation (Scheme 1). These two anions have different reactivity. One anion (anion 1) is less reactive (or unreactive) with alkyl halides or tosylate, and the other anion (anion 2) is more reactive to halides or tosylate and takes part in the cyclization. The use of these dianions for the cyclization has the following characteristic points.

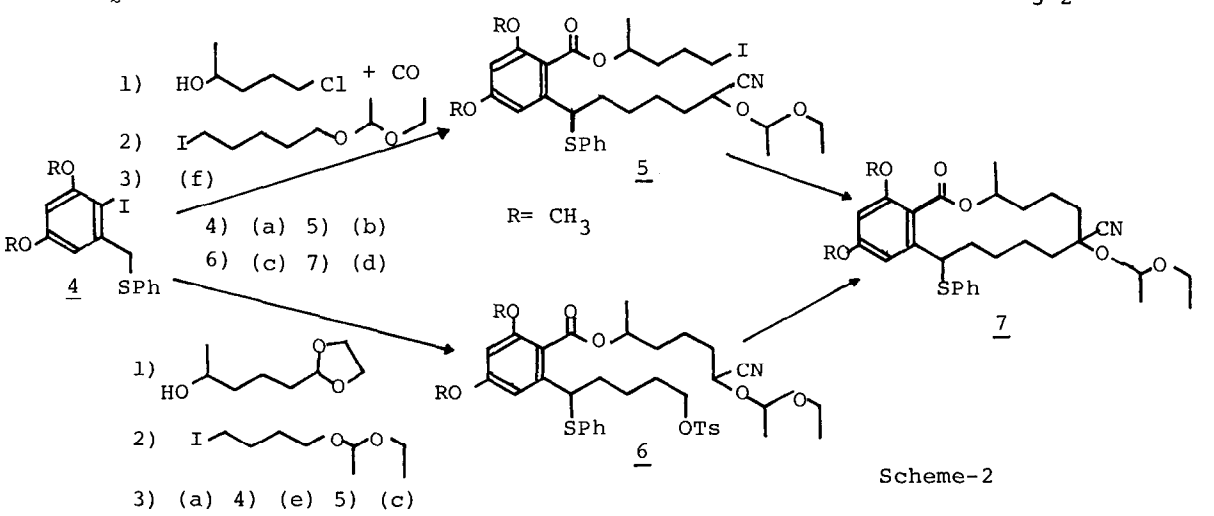


Scheme-1

(1) The anion 1 controls the conformation or orientation of the side chains, making the approach of the reaction centers easier. (2) The anion 1 protectes the neighboring or conjugated ester group from nucleophilic attack by electronic and steric effects before and after the cyclization. (3) Presence of two negatively charged carbons in the same molecule gives larger intermolecular ionic repulsion and hence chances of intermolecular reaction decrease. This feature is particularly superior to the commonly used activated ester method. By virtue of the higher intermolecular repulsion, it is not necessary to carry out the cyclization reaction under high dilution condition.

In order to prove the above mentioned speculation by experiments we selected phenylthio group (Z = SPh) for the activation of the anion 1 and the protected cyanohydrin (Y, Y = CN, OR) for the anion 2. This methodology, if successful, can offer a highly efficient general synthetic method for a number of naturally occurring macrolides such as zearalenone, lasiodiplodin, hypothemycin, and curvularin. We wish to report here the dianion effect in the synthesis of zearalenone by us and others. The first one is the intramolecular esterification method.[5] The second one is the intramolecular alkylation of ω-haloalkyl 2-phenylthiomethylbenzoate.[2c] The third one is the intramolecular alkylation of the protected cyanohydrin.[3b] We have attempted to synthesize zearalenone 10b by the alkylation using dianions 5 and 6.

Preparation of the protected cyanohydrins 5[6] and 6[7] was carried out as shown in Scheme 2 by applying the method previously developed in this laboratory [Palladium catalyzed carbonylation[8] of 1-iodo-2-phenylthiomethyl-4,6-dimethoxybenzene (4) and the alkylation[2b,2c] of the resulting ester using $KN(SiMe_3)_2$].



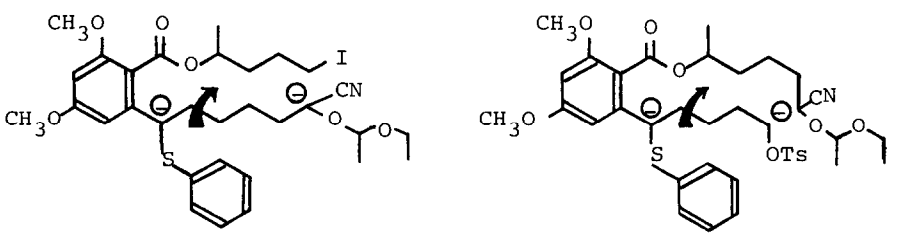
Scheme-2

(a) H_3O^+ (b) CrO_3/Py (c) $NaHSO_3$/NaCN (d)  /H_3O^+

(e) p-TsCl/Py (f) KI/HMPA

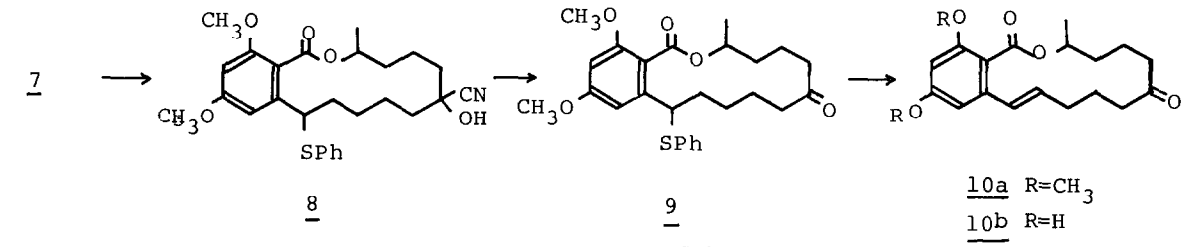
The cyclization of 5 was carried out in the following way. The protected cyanohydrin 5 (136.3 mg, 0.2 mmol) in THF (5 mL) was added, using a Hershberg dropping funnel, over 30 min at 40°C under a nitrogen atmosphere to $NaN(SiMe_3)_2$ (1 mmol) in THF (15 mL) (procedure A). The reaction mixture was quenched with sat. aq. NH_4Cl solution. The cyclized product 7[9] was isolated in 95% yield after short column chromatographic purification. The more convincing evidence for the dianion effect was obtained by the reverse addition method (procedure B). In this procedure, a solution of $NaN(SiMe_3)_2$ (0.5 mmol) in THF (2.5 mL) was added over 40 min to a solution of 5 (0.1 mmol) in THF (8 mL). Although the base was added to 5 at its rather high concentration, the intermolecular reaction was not observed and the cyclized product 7 was obtained in 78% yield. Then the cyclization of 6 was carried out by the procedure A and only the 14-membered lactone 7 was obtained in 82% yield. The formation of five-membered ring by the reaction of the benzyl anion and tosylate in 6 was not observed.

In these cyclization reactions, the concentration of the substrate at the end of the reaction was ten-times higher and also the dropping was sixteen-times faster than the activated ester method.[5c] But no product of the intermolecular reaction was obtained. This result can be explained by the above consideration. The initial formation of carbanion was at the benzyl position[10] which controls the orientation of the side chain favorable for the cyclization. The phenylthio group, moreover, should become a blocking group for free rotation of the side-chain as shown in Scheme 3. These effects lead to the high yields of 7. The presence of two negative charges in the same molecule causes intermolecular repulsion, and hence inhibits intermolecular reaction.



Scheme-3

The cyclization product 7 was converted to the dimethyl ether of zearalenone 10a in the following way (Scheme 4). Acid treatment of 7 (3 N HCl/THF, 0°C) and base treatment (2% NaOH/Et_2O, 0°C for 1 min) of the resulting cyanohydrin 8 gave the ketone 9[11] in 95% overall yield without the internal translactonization or hydrolysis of the ester. The oxidative removal of the phenylthio group ($NaIO_4$, toluene reflux for 20 min) gave 10a in 85% yield which showed the identical NMR and IR spectra with those of an authentic sample prepared in this laboratory.[2c] Further application of this method to the syntheses of more complex macrolides with various fuctionalities is in progress.



Scheme-4

References and Notes

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6. IR (film) 1710 cm^{-1}; NMR (CCl_4) δ 2.85-3.29 (m, 2 H, CH_2I), 3.30-3.60 (m, 2 H, OCH_2), 3.72 (bs, 6 H, OCH_3), 3.95-4.45 (m, 2 H, OCHCN and benzyl), 4.76 (m, 1 H, OCHO), 4.80-5.35 (m, 1 H, HCO), 6.19 (bs, 1 H, aromatic), 6.55 (bs, 1 H, aromatic), 7.10 (bs, 5 H, aromatics).
7. IR (film) 1710 cm^{-1}; NMR (CCl_4) δ 2.44 (s, 3 H, Ar-CH_3), 3.79 (s, 6 H, OCH_3), 6.38 (bs, 1 H, aromatic), 6.63 (bs, 1 H, aromatic), 7.25 (bs, 5 H, aromatics), 7.39 (d, J = 8 Hz, 2 H, aromatics), 7.81 (d, J = 8 Hz, 2 H, aromatics).
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9. IR (film) 1710 cm^{-1}; NMR (CCl_4) δ 3.72 (s, 6 H, OCH_3), 6.20 (bs, 1 H, aromatic), 6.54 and 6.78 (bs, 1 H, aromatic), 7.10 (bs, 5 H, aromatics).
10. The quenching with D_2O, when one equiv. of $NaN(SiMe_3)_2$ was added to 5 at 40°C, gave the benzyl deuterio product.
11. IR (KBr) 1709, 1603, 750 cm^{-1}; NMR (CCl_4) δ 1.34 (d, J = 6 Hz, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.45 (t, J = 6.3 Hz, 1 H, benzyl), 5.02-5.69 (m, 1 H, HCO), 6.39 (bs, 1 H, aromatic), 6.87 (bs, 1 H, aromatic), 7.05-7.64 (m, 5 H, aromatics). MS m/e 456 (M^+); Anal. Calcd: C, 68.39; H, 7.06. Found: C, 68.08; H, 7.02.

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