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NEW REAGENTS FOR THE CONVERSION OF HYDROXY ACIDS TO MACROLACTONES BY THE DOUBLE ACTIVATION METHOD

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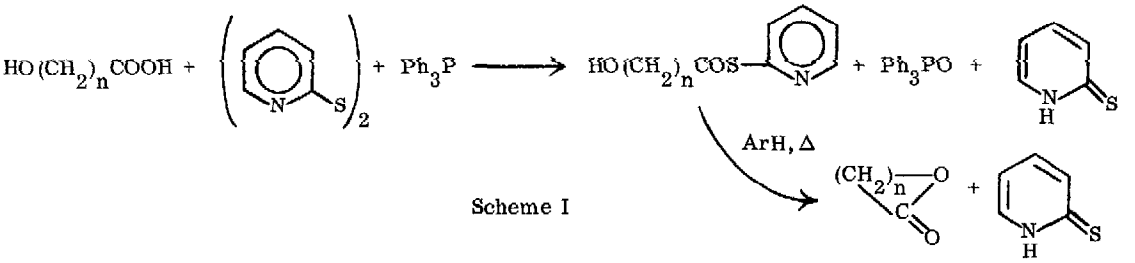
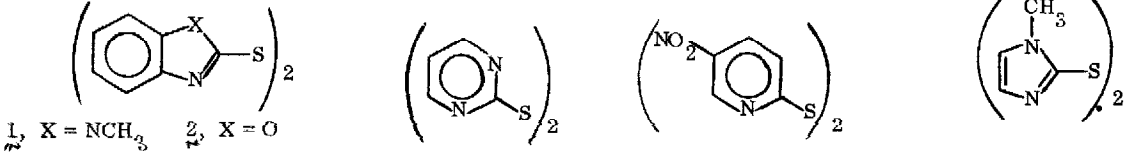
We have previously described a successful strategy for the cyclization of long chain hydroxy acids to macrocyclic lactones which depends on the simultaneous activation of both hydroxyl and carboxyl functions.[1] In addition a wide variety of applications[2-4] of the method and a study of reaction mechanism[5] have been presented. The key reaction in this research was the thermal cyclization of an ester of 2-pyridinethiol with a hydroxy acid in benzene, toluene or xylene as solvent (usually at reflux temperature) to form lactones and 2-pyridinethione (Scheme I). Since the double activation process can be effected under neutral conditions in non-polar solvent, it is applicable to sensitive polyfunctional molecules, a cardinal advantage in applications such as syntheses of macrolide antibiotics. Despite the generally superior results obtained in the lactonization of 2-pyridinethiol esters, we have sought to extend the investigation to other thiol esters with the objective of finding the ultimate with regard to speed and efficiency of cyclization. This note reports a significant advance in this direction based upon the use of various bis-2-imidazolyl disulfides as reagents.



Scheme I

A survey was made of a variety of heterocyclic disulfides which in principle are capable of reacting in the same way as 2,2'-dipyridyl disulfide[1,5] (Scheme I) to convert hydroxy acids to lactones. Most of these were either totally ineffective as reagents (e.g., disulfides 1-3) or less satisfactory than 2,2'-dipyridyl disulfide (e.g., disulfides 4 or its 6-nitro derivative, and 5). However, an extraordinarily interesting and promising result was obtained with bis-1-methyl-2-imidazolyl disulfide (6).



1, X = NCH_3 2, X = O

4, X = S

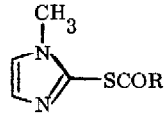
3

5

6

When a mixture of 6, Ph_3P and 16-hydroxyhexadecanoic acid (1.5:1.5:1 equiv) in benzene was allowed to react, the formation of hexadecanolide in yields of 20-37% (depending on concentration) could be detected (by vpc analysis or isolation) after only 10 min at 25°. However, subsequent to this period no further lactone

formation occurred either upon heating or prolonged reaction at 25° (up to 48 hr). Aqueous workup of the reaction mixture resulted in the isolation of ca. 60% of the starting 16-hydroxyhexadecanoic acid. Another experiment revealed that the recovered hydroxy acid is actually formed during the aqueous workup by hydrolysis of a reactive intermediate. Thus storage of a mixture of 6, Ph_3P and 16-hydroxyhexadecanoic acid in benzene at 25° for 2 hr to ensure complete lactonization and treatment with excess aniline at 25° for 2 hr led, after aqueous workup, to isolation of a 20% yield of lactone and a 52% yield of the anilide of 16-hydroxyhexadecanoic acid. Since neither the lactone nor starting hydroxy acid react with aniline under these conditions it is clear that the reaction of 6, Ph_3P and 16-hydroxyhexadecanoic acid must produce two different activated acyl derivatives, only one of which can serve as a precursor of lactone. Clearly the two activated species cannot be in rapid equilibrium. It seemed reasonable to formulate these species as the isomeric S-acyl and N-acyl structures, 7 and 8 respectively, and this view was supported by other lines of evidence.



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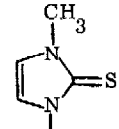
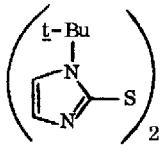


8

Reaction of 6, Ph_3P and n-heptanoic acid in methylene chloride for only 1 min at 25° resulted in complete disappearance of heptanoic acid as shown by infrared analysis (loss of absorption due to -COOH at 1705 cm^{-1}) with the formation of species having infrared absorption at 1730 cm^{-1}. Since both 7 and 8 are expected to show carbonyl absorption at 1730 cm^{-1}, infrared analysis does not disclose the relative amounts present. Reaction of 6, Ph_3P, methanol (20 equiv) and heptanoic acid in benzene for 30 min followed by aqueous workup and isolation gave methyl heptanoate in 20% yield with the balance accounted for as heptanoic acid. In contrast, reaction of 6, Ph_3P and heptanoic acid in benzene for 30 min followed by treatment with excess methanol for 30 min and then aniline (5 equiv) for 30 min gave mainly heptanoic anilide (91% isolated yield). Finally, keeping a solution of 6, Ph_3P and heptanoic acid in benzene for 30 min followed by exposure to excess methanol (for 30 min) and isolation gave only 1.5% of methyl heptanoate. It is clear from these results that the two carboxyl activated species are formed in a proportion of roughly 25:75 with the minor component capable of reaction with either methanol or aniline and the major component reactive toward aniline but not methanol. Further, the minor component appears capable of rearrangement to the major component, but not vice versa. Evidence that the minor component corresponds to the thioester species 7 was obtained from the study of the two imidazole reagents 9 and 10.



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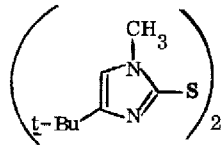

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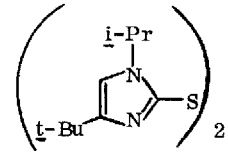
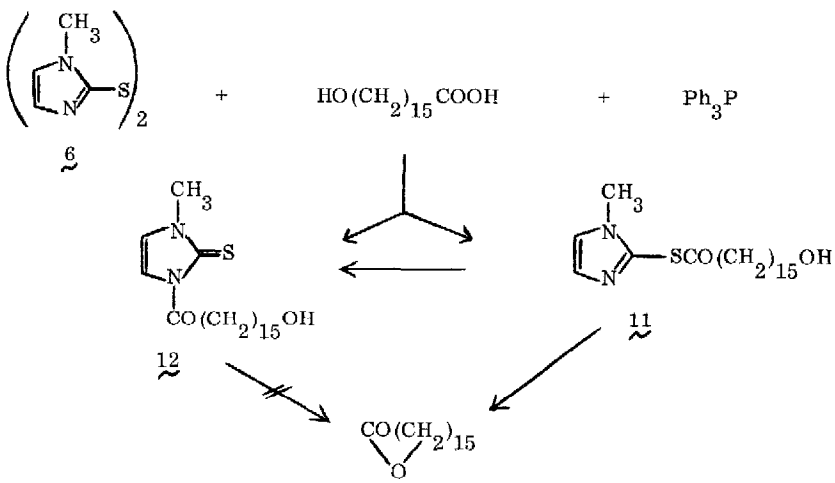


13

The reasonable assumption was made that for steric reasons the t-butyl group of 9 would somewhat disfavor formation of the thioester whereas the t-butyl group of 10 would strongly disfavor formation of the

N-acyl imidazole system. Both reagents (1.5 equiv) were treated with Ph_3P (1.5 equiv) and 16-hydroxyhexadecanoic acid (1.5 equiv) in benzene. The results using 9 as reagent were similar to those obtained with the N-methyl analog 6, i.e., lactone was formed in only low yield (17-30%). The reaction with reagent 10 was considerably slower than with either 6 or 9 (and proceeded best at 50°), but gave hexadecanolide in much higher yield (78-91%, the highest yield being realized when the hydroxy acid was added slowly to the reaction mixture). These results indicate that lactone is formed from an S-acyl rather than an N-acyl precursor and lead to Scheme II to explain the results obtained with 6. In addition, observations made on the reaction of 6-hydroxy-n-hexanoic acid with the reagent 6 and Ph_3P indicate that most of the N-acyl imidazole intermediate (8) formed at short reaction times (<10 min) is generated directly and not by rearrangement of the S-acyl intermediate (7).



Scheme II

Specifically, reaction of 6-hydroxy-n-hexanoic acid afforded only ca. 25% of the corresponding lactone, i.e., an amount quite comparable to that formed under the same conditions from 6 and 16-hydroxy-n-hexadecanoic acid. *Since the rate of lactonization of the 2-pyridinethiol ester of the C_6-hydroxy acid is roughly 100 times* greater than that of the C_{16}-hydroxy acid, the similar yields of lactone obtained with reagent 6 argues that the extent of lactonization in each case is determined mainly by the relative amounts of S-acyl and N-acyl intermediates initially formed from 6, rather than by closely competitive lactonization and S→N acyl migration of a common S-acyl precursor.

The mechanistic features of the lactonization of hydroxy acids using 2-imidazolyl disulfide reagents can be summarized. 1) In the case of 6 both S-acyl and N-acyl intermediates are independently generated, with all lactone being derived from the former. 2) The S-acyl and N-acyl intermediates are not in rapid equilibrium, although a relatively slow S→N acyl rearrangement can be detected. 3) Formation of N-acyl intermediate is effectively inhibited in the case of reagents such as 10 which are characterized by strong steric screening at N(3).

The 4-t-butyl-substituted imidazole reagents 10 and 13, in fact, have proven to be clearly superior to 2,2'-dipyridyl disulfide for the lactonization of long-chain hydroxy acids in two important respects: (1) lower

reaction temperatures may be used (generally 80°, refluxing benzene), and (2) higher yields are usually obtained. For example, the following lactones were generated from the corresponding ω-hydroxy acids using 13 as reagent in the indicated yields: tetradecanolide (90%), hexadecanolide (96%), dodecanolide (87%) (cf. ref. 1). At 80° the relative rates of cyclization of the thiol esters of 16-hydroxy-n-hexadecanoic acid formed using as reagent 13, 10 or 2,2'dipyridyl disulfide were found to be 100:60:1, respectively. Reagent 13, which is highly effective and easily made, was prepared as follows.

2,2'-Bis-(4-t-butyl-N-isopropyl)imidazolyl Disulfide (13). A solution of 53.7 g (0.300 mole) of α-bromopinacolone (from pinacolone and 1 equiv of bromine) in 100 ml of benzene was added dropwise over 30 min to a solution of 130 ml (1.5 mole) of isopropylamine in 50 ml of benzene at 0°. After complete addition, the reaction mixture was stirred at 0° for 1 hr, then poured onto ice. After addition of 56 g (1 mole) of KOH with stirring, the amino ketone was isolated by extraction with benzene, drying ($MgSO_4$) and evaporation (41.4 g, 88%). The product could be distilled (b.p. = 54-55°/4 mm), but generally was used in crude form.

The crude amino ketone (0.269 mole) was dissolved in 125 ml of ethanol, to which was added potassium thiocyanate (30.7 g, 0.316 mole) and 2.0 N HCl (150 ml). The resulting solution was heated at reflux for 16 hr, after which a dense crystalline precipitate had formed. After addition of water (100 ml) and cooling to ambient temperature, the product was removed by suction filtration and dried, yielding 4-t-butyl-N-isopropyl-2-mercaptoimidazole (42.60 g, 72% from α-bromopinacolone). Recrystallization (EtOAc) gave 39.80 g of rhomboid crystals, m.p. 263-264°. Pmr ($CDCl_3$): 1.28 (s, 9H, t-butyl), 1.35 (d, J=6.5 Hz, 6H, i-propyl methyls), 5.02 (septet, J=6.5 Hz, 1H, i-propyl methine), 6.35 (d, J=2 Hz, 1H, 5-imidazole proton), and 12.15 δ (broad m, 1H, S-H proton).

A solution of 4-t-butyl-N-isopropyl-2-mercaptoimidazole (19.80 g, 0.100 mole) in dry THF (175 ml) under N_2 was cooled to -78° and treated with n-butyllithium in hexane (2.29 M, 43.6 ml). Complete solution did not occur until the slurry was warmed to room temperature. At ambient temperature, a solution of iodine in THF was added until a faint orange color of I_2 persisted (13.5 g I_2 in 15 ml THF). After stirring an additional 30 min, the solution was poured into 200 ml of 5% brine and extracted into two 75 ml portions of CH_2Cl_2. Drying ($MgSO_4$) and evaporation gave 19.55 g (99%) of the disulfide (pure by pmr analysis). Recrystallization from ligroine gave 18.74 g of fine yellow needles, m.p. 153-153.5°.

The application of the effective new reagents developed in this study (10 or 13) to macrocyclic lactone formation can be illustrated by the following procedure.

Hexadecanolide. A dry 10 ml flask (N_2 atmosphere) was charged with 16-hydroxyhexadecanoic acid (54.4 mg, 0.200 mmol), 2,2'-di(4-t-butyl-N-isopropyl)imidazole disulfide (120 mg, 0.30 mmol) and triphenyl phosphine (79 mg, 0.30 mmol). Dry toluene (2 ml) was added, and the reaction was stirred at 0° until the yellow disulfide color faded (15 min). The solution was diluted to 20 ml with dry toluene, placed in a cryocooled syringe, and added to 40 ml of refluxing benzene via mechanical syringe drive over 4 hr. After complete addition, the solution was heated at reflux for an additional 2 hr. Vpc analysis on a 6 ft 3% OV-17 column at 175° indicated a 96% yield of hexadecanolide. The solution was cooled, filtered through 5 g of silica gel (washing with CH_2Cl_2) and evaporated. Chromatographic separation on silica gel gave 42.2 mg (83%) of pure hexadecanolide, identical with an authentic sample.

[6] This research was assisted financially by a grant from the National Institutes of Health.

References and Notes

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