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ACYLATION OF LITHIUM Z-β-LITHIOACRYLATES: APPLICATION TO A SHORT SYNTHESIS OF LEPIOCHLORIN[1]

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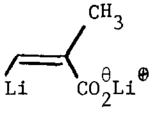
ABSTRACT: Studies on the acylation of lithium Z-β-lithioacrylates including a short synthesis of lepiochlorin are described.

Recently, we reported convenient syntheses of α,β-butenolides[2] and β-bromo-α,β-butenolides[3] by reactions of lithium Z-β-lithioacrylates, e.g. 1, or lithium E-β-bromo-β-lithioacrylates, e.g. 2, with aldehydes and ketones followed by acidification of the resulting adducts. We now wish to report the results of studies on the acylation of reagents such as 1 and 2, including the application of this methodology to a short synthesis of lepiochlorin (3b), an antibiotic which has been isolated from a laboratory-grown *Lepiota* fungus.[4]



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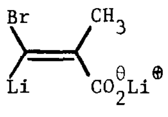

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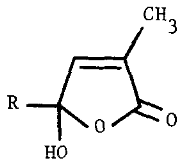
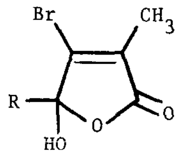


3 a. R = CH_3
b. R = CH_2Cl



4 a. R = CH_3
b. R = CH_2Cl
c. R = Ph

Acylations were accomplished in low yields with acetic anhydride and chloracetic anhydride by dropwise addition of a solution of the organolithium reagent 1 in diethyl ether at -78°, prepared as described previously,[2] to a stirred ethereal solution containing 2 equiv. of the anhydride at -78° under nitrogen, stirring of the mixture for 3 h. at -78°, and then acidification with cold 3 N hydrochloric acid. This led to the isolation of mixtures containing mainly methacrylic acid and the γ-hydroxybutenolides 3. Rapid washing of these mixtures with a cold saturated sodium bicarbonate solution allowed removal of the acid,[5] and the butenolides were further purified by recrystallization or by preparative thin layer chromatography (TLC) on silica gel. Butenolide 3a, which had identical physical properties to those previously reported,[6] was obtained in 25% yield, while butenolide 3b, which showed identical spectral properties and TLC behavior to an authentic sample of lepiochlorin,[7] was obtained in 20% yield.

Butenolide 3a could not be isolated when acetyl chloride was employed for the acylation of 1 and likewise 3b was not obtained when acylations of 1 with chloroacetyl chloride or ethyl chloroacetate were attempted. Also, attempted conversion of 1 to the corresponding organocuprate by treatment of the solution with 0.5 equiv. of the cuprous bromide-dimethyl sulfide complex[8] and then addition of the solution to an acetyl chloride solutions did not yield butenolide 3a. The recovery of significant amounts of methacrylic acid in all the runs including the successful ones indicated that reagent 1 behaved as a base rather than a nucleophile toward the relatively acidic acylating agents described above.

The β-bromo lithioacrylate 2 appears to be less basic and more nucleophilic toward the anhydride acylating agents than 1, presumably because of the electron withdrawing effect of the bromine atom. Thus when solutions of 2 in THF at -78°, prepared as described previously,[3] were reacted with 2 equiv. of acetic anhydride or chloroacetic anhydride as described for 1, β-bromo-γ-hydroxybutenolides 4a[9] and 4b[9] were isolated in 45% and 36% yields, respectively. The recovery of significant quantities of β-bromomethacrylic acid in these runs indicated that deprotonation of the acylating agent also competed with nucleophilic attack on the carbonyl group to some extent. Reaction of 2 with benzoyl chloride which contains no α protons gave butenolide 4c[9] in 65% yield.

Selective hydrogenolysis of the vinyl bromide in butenolide 4b provided an alternative method of preparation of lepiochlorin. Thus when a solution of 4b in ethyl alcohol containing a few drops of quinoline over a 5% palladium-on-barium sulfate catalyst was allowed to take up 1-2 equiv. of hydrogen at atmospheric pressure, 3b isolated in 30% yield by preparative TLC of the reaction mixture.

While the one- and two-step routes described above led to the production of lepiochlorin in relatively low yields, they have an advantage of being quite short. Donaubauer and McMorris[10] have recently reported a six-step synthesis of this natural product from the epoxide of allylmethoxyethoxymethyl ether and 2-phenylthiopropanoic acid in 25-30% overall yield.

References and Notes

1. This research was supported in part by a grant (NSF#7810044) from the National Science Foundation for which we are grateful.
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7. We are grateful to Dr. M. S. R. Nair for supplying us an authentic sample of lepiochlorin.
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