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AN IMPROVED REAGENT FOR THE O-ALKYL CLEAVAGE OF METHYL ESTERS BY NUCLEOPHILIC DISPLACEMENT

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Various reagents have been developed for effecting cleavage of the alkyl oxygen bond of methyl esters by nucleophilic displacement of the carboxylate anion from the methyl group. Of these, the most widely used methods have been: lithium iodide in refluxing pyridine, 2,6-lutidine, or 2,4,6-collidine;[1] lithium iodide in hot dimethylformamide (DMF);[2] and potassium t-butoxide in warm dimethylsulfoxide (DMSO).[3] This type of reagent is advantageous in cases where the usual aqueous hydrolytic conditions either fail to effect cleavage because of steric hindrance at the carbonyl group, or are precluded because of the presence of acid- or base-sensitive functionalities.

Now we wish to disclose that lithium n-propyl mecaptide in hexamethylphosphoramide (HMP) is an especially effective reagent for the cleavage of methyl esters under mild conditions. The reaction proceeds readily at room temperature, and the product is easily isolated. Thus we have put into practice an observation made in a mechanistic study by Vaughan and Baumann,[4] namely that sodium n-propyl mercaptide in DMF effects ready cleavage of esters by an S_N2 process. By using the lithium instead of the sodium salt and HMP instead of DMF, we have shown that the rate of cleavage of methyl mesitoate is enhanced by a factor of about 57. The application

of our reagent to the cleavage of four esters is described below.

The reagent is prepared by adding freshly distilled n-propyl mercaptan (1.0 ml.) to a suspension of finely ground lithium hydride (0.3 g.) in dry, oxygen-free HMP (10 ml.) under an inert atmosphere, stirring at 25° for 1 hr followed by filtration without contact with air. The reagent is stored at 0° under argon pressure without removal of the excess mercaptan. The concentration of mercaptide is typically 0.5-0.6 M. Contact with oxygen results in rapid oxidation of the mercaptide[5] and is to be avoided.

Methyl mesitoate is the classic example of a hindered ester. Using our reagent (0.0443 M) and methyl mesitoate (0.0378 M), and following the reaction by vapor phase chromatography, we found a half-life of 3 min at 34.5°. Using the rate constant for the reaction of this ester with sodium n-propyl mercaptide in DMF at 34.2°,[4] we calculate that this corresponds to a half-life of about 170 min for the same initial concentrations of reagents.

A solution of 212.4 mg. of methyl mesitoate in 8.5 ml. of 0.54 M (3.9 equiv.) mercaptide reagent was kept under nitrogen for 1.25 hr at 25°, then transferred into 150 ml. of 1 N HCl. Extraction with ether gave a crude product, which was dissolved in 2 N NaOH, washed with ether, and reprecipitated with HCl to give 195.1 mg. (100% yield) of colorless crystals, m.p. 148-151°.* Two recrystallizations from 50% ethanol-water gave material, m.p. 153-154° (lit.[6] 153-154°), which was identical by mixed m.p. and IR with authentic mesitoic acid.

Methyl O-methylpodocarpate requires extremely severe conditions for ordinary hydrolysis.[7] It was used as an example for cleavage with the potassium t-butoxide/DMSO reagent, and required 2 hr at 56°.[3]

Methyl O-methylpodocarpate (114.3 mg.) was treated with 3.5 ml. of 0.63 M (5.8 equiv.) mercaptide reagent for 1.5 hr at 25° to give 108.8 mg. (100% yield) of colorless crystals, m.p. 156.5-158°. One recrystallization from petroleum ether gave material, m.p. 157.5-158.5° (lit.[3] 158-161°), which was reconverted with diazomethane to the ester, m.p. 126-127.5°,

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* For melting point determinations, all samples, with the exception of the podocarpate derivatives, were sealed in capillary tubes.

identical with the authentic starting material by mixed m. p. and IR. **

Reaction of the potassium t-butoxide/DMSO reagent with methyl triisopropylacetate has also been examined. The cleavage of this highly hindered ester required 4 hr at 100°.[3]

Triisopropylacetic acid (8. 6 mg.) was esterified with diazomethane, and the crude ester was treated with 0. 5 ml. of 0. 55 M (6. 0 equiv.) mercaptide reagent for 3. 5 hr at 25° to give 8. 5 mg. (99% yield) of colorless crystals, m. p. 137-140°. One recrystallization from methanol-water (75% recovery) gave material, m. p. 148-149° (lit.[3] 150-151. 5°), which was identical by mixed m. p. and IR with an authentic specimen of triisopropylacetic acid.

Methyl 3β-acetoxy-Δ^5-etienate contains both a hydrolytically sensitive functionality and a relatively hindered ester group, and was used in the investigation of the lithium iodide/refluxing lutidine system as a selective ester cleavage reagent.[1] With both iodide and mercaptide, S_N2 displacement of the acetate group is sterically hindered and attack at the acetate carbonyl is energetically unfavorable; therefore, reasonable selectivity can be realized. After 8 hr reflux, the lithium iodide method gave 25-28% of starting material, 49-51% of the desired acetoxy acid, and 5-10% of the hydroxy acid resulting from hydrolytic loss of the acetate group.[1]

A solution of 172. 9 mg. of the acetoxy ester in 0. 90 ml. of dry HMP and 0. 89 ml. of 0. 58 M (1. 1 equiv.) mercaptide reagent was kept under nitrogen for 24 hr at 25°. The relatively long reaction period was required because of the limited amount of reagent used. The reaction mixture was transferred into 100 ml. of ice water containing 1 ml. of 1 N HCl. Extraction with ether gave 166. 0 mg. of crude product, which was chromatographed on 5 g. of silica gel. Elution with 5% ether-benzene gave 144. 2 mg. of pure acetoxy acid; more polar fractions contained hydroxy acid as well. The impure fractions containing acetoxy acid (total 18. 0 mg.) were purified by preparative TLC to give another 8. 7 mg. The total yield of 3β-acetoxy-Δ^5-etienic acid was 152. 9 mg. (92% yield), m. p. 242-246°. One recrystallization from methanol gave material, m. p. 244-245° (lit.[1] 245-247°), which was identical with authentic acetoxy acid by mixed m. p. and IR.

** Recently Feutrill and Mirrington[8] reported their use of ethyl mercaptide in hot DMF for demethylation of aryl methyl ethers. While this reaction proceeded readily at 100° with our reagent, no cleavage of the podocarpate ether was detected by NMR under the mild conditions used for the cleavage of the ester.

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