Tetrahedron Letters No. 38, pp 3987 - 3990, 1972. Pergamon Press. Printed in Great Britain.

INDUCEMENT OF ONE-STEP DEHYDROBROMINATION-DECARBOMETHOXYLATION AND O-ALKYL CLEAVAGE OF METHYL ESTERS BY 1,5-DIAZABICYCLO[4.3.0]NONENE-5(DBN)

D. Howard Miles and Edward J. Parish[1]

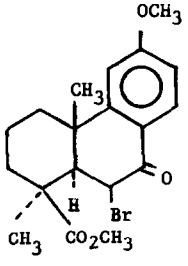
Department of Chemistry, Mississippi State University

State College, Mississippi 39762

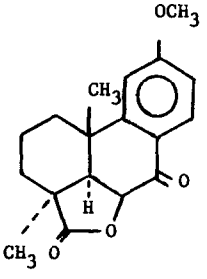
(Received in USA 31 July 1972; received in UK for publication 21 August 1972)

We wish to report the one-step conversion of bromo-ketone I to the α, β unsaturated ketone V. The present preliminary communication also describes basic studies which indicate that 1,5-diazabicyclo[4.3.0]nonene-5(DBN) is useful as a reagent for the O-alkyl cleavage of methyl esters.

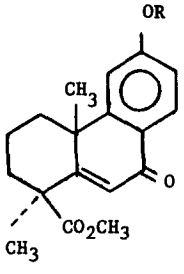
While exploring new synthetic approaches to diterpenoid intermediates bromo-ketone I was prepared from podocarpic acid according to known procedures.[2,3] Since the synthesis of lactone II is a key step in our synthetic scheme, the preparation of II in high yield from I was desirable. Wenkert, et al.,[3] have reported the transformation of bromo-ketone I to a mixture of lactone II (47% yield) and ester III (40% yield) by refluxing in excess collidine for two hours.



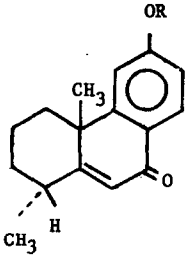
I



II



III, R = CH_3
IV, R = H



V, R = CH_3
VI, R = H

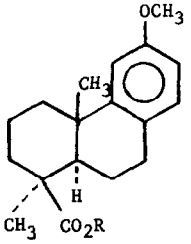
When bromo-ketone I was treated with sodium methoxide only elimination product III was obtained.[3] It was suggested that a major factor in the contrasting behavior of sodium methoxide and collidine toward I might be the steric requirements of the bases for proton abstraction.

The base 1,5-diazabicyclo[4.3.0]nonene-5(DBN) was chosen for the initial investigation into the improvement of the yield of lactone II because of its greater steric requirements as compared

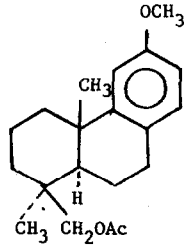
with collidine. Consequently, bromo-ketone I (500 mg) was treated with 472 mg (3.0 equiv) of DBN dissolved in 1.51 ml of o-xylene at reflux (165°C) for six hours. The ether extract of the acidified reaction mixture was washed with 5% aqueous sodium carbonate and water, dried over anhydrous sulfate, and evaporated in vacuo. Crystallization of the residue from 20:1 methylene chloride-methanol souution yielded 302 mg (93%) of a white crystalline compound [m.p. 122.5-123.5°C; λ_{max}^{KBr} 1650, 1600 cm^{-1}; $\delta_{ppm}^{CHCl_3}$ 1.41(3H, d, J=6cps), 1.73(3H), 4.33(3H), 6.91(1H, d, J=1.8cps), 7.39(2H, multiplet), 8.98(1H, d, J=9cps)]. Examination of the NMR and IR spectra allowed assignment of structure V.* Neither of the expected products, lactone II and elimination product III, were found.

Additional evidence for the structure V was provided by the conversion of postulated intermediate III to V in 78% yield by treatment with DBN in a similar manner. Since DBN is known to be a facile dehydrohalogenating agent,[4-8] the transformation of III to V lends support to the postulation that V might have arisen, in one step, from I by dehydrobromination and subsequent decarbomethoxylation. This conversion has previously been reported to require two relatively low yield steps.[3] Support for the stereochemistry assigned to V is provided by the report[3] that VI can be obtained from IV in approximately 33% yield by dealkylation and subsequent decarboxylation with lithium iodide in refluxing collidine.[9,10] Treatment of either III or IV with decarbomethoxylation reagents gives low yields of V (78%) and VI (33%) in sharp contrast to the high yield (93%) of V obtained from I by the method we are reporting in this communication.

Evidence that decarbomethoxylation of compounds I and III proceeded through O-methyl cleavage of the methyl ester and subsequent decarboxylation was provided by the following results. Treatment of ester IX (500 mg) with 103 mg (5.0 equiv) of DBN in 1.12 ml of o-xylene at reflux (165°C) for six hours followed by the usual work-up yielded 368 mg (91%) of pure white crystalline acid X



IX, R = CH_3
X, R = H



XI

*All analyses were within acceptable limits of calculated values.

[m.p. 159-160°C(lit[11] m.p. 158-161°C); λ_{max}^{KBr} 3200-2500, 1600, 1460 cm^{-1}; $\delta_{ppm}^{CHCl_3}$ 1.37(3H), 1.72 (3H), 4.20(3H), 7.35(3H, multiplet), 12.65(1H)]. When acetate XI was treated with DBN in the same manner only starting material could be recovered from the reaction mixture. These results rule out the possibility that the conversion of ester IX to acid X could have proceeded by the hydrolytic route. If this had been operative acetate XI would have been easily cleaved in comparison to ester IX. Ester IX (methyl o-methylpodocarpate) requires extremely severe conditions for ordinary hydrolysis.[12]

The generality of the cleavage reaction is demonstrated by the application of DBN to the cleavage of methyl o-methylpodocarpate (IX) and the three esters described below.

Methyl mesitoate is the classic example of a hindered estet. A solution of DBN (870 mg, 5.0 equiv) and methyl mesitoate (250 mg) in 1.01 ml of o-xylene was refluxed at 165°C for six hours. Work-up in the usual manner gave 216 mg (94% yield) of colorless crystals, m.p. 149-151°C. Two recrystallizations from 50% ethanol-water gave material, m.p. 153-154°C(lit[13] 153-154°C), which was identical by mixed m.p., and IR with authentic mesitoic acid.

Methyl triisopropylacetate has also been utilized to confirm the ability of several reagents to cleave hindered esters.[11,14]

Triisopropylacetic acid (100 mg) was esterified with diazomethane, and the crude ester was treated with DBN (334 mg, 5.0 equiv) in 0.38 ml of o-xylene at 165°C for six hours to give 94.2 mg (94% yield) of colorless crystals, m.p. 136-139°C. One recrystallization from methanol-water gave material, m.p. 149-150°C(lit[11] 150-151.5°C), 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. With both iodide and DBN S_N2 displacement of the acetate group is sterically hindered and attack at the acetate carbonyl is energetically unfavorable; therefore, reasonable selectivity can be achieved. After eight hours 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.[10]

A solution of DBN (258 mg, 4.0 equiv) and the acetoxy ester (200 mg) in 0.37 ml o-xylene was refluxed for two hours at 165°C. The relatively short reaction time was utilized in order to maximize the selectivity. The usual work-up yielded 154 mg of crude product. GLC comparison

with authentic samples showed that the DBN method gave 27% of starting material, 56% of the desired acetoxy acid, 7% of the hydroxy acid resulting from hydrolytic loss of the acetate group,[10] and 5% of the diene acid resulting from elimination of the acetate group. Based on the material reacted, reasonable selectivity (77%) was achieved.

Reagents such as lithium iodide in refluxing pyridine, 2,6-lutidine, or 2,4,6-collidine;[10] lithium iodide in hot dimethylformamide;[15] potassium t-butoxide in DMSO;[11] and lithium ethyl mercaptide in hexamethylphosphoramide[14] have been developed for effecting cleavage of methyl esters by nucleophilic displacement of the carboxylate anion from the methyl group. Although DBN does not cleave esters under the mild conditions reported for the mercaptide[10] and potassium t-butoxide methods,[11] this is the first report, to our knowledge, of the cleavage of methyl esters without the utilization of ionic nucleophilic reagents.

Acknowledgements. We wish to thank the graduate school and the Biological and Physical Sciences Institute for partial financial support. We express our sincere appreciation to Dr. Ian K. Walker, Department of Scientific and Industrial Research, Wellington, New Zealand, for generous supplies of podocarpic acid. We wish to thank Dr. J. B. Nabors for numerous helpful discussions.

REFERENCES

1. National Defense Education Act Graduate Fellow, 1971-1973.
2. E. Wenkert, et al., J. Org. Chem., 30, 713 (1965).
3. E. Wenkert, et al., Canad. J. Chem., 41, 1924 (1963).
4. E. Truscheit and K. Eiter, Ann, 65, 658 (1962).
5. E. Vogel, R. Schubart, and W. A. Boll, Angew. Chem. Internat. Ed., 3, 510 (1964).
6. K. Eiter and H. Oediger, Ann, 682, 62 (1965).
7. H. Oediger, H. J. Kable, F. Moller, and K. Eiter, Ber., 99, 2012 (1966).
8. E. Vogel and F. G. Klarner, Angew. Chem. Internat. Ed., 7, 374 (1968).
9. E. Taschner and B. Liberek, Roczniki Chem., 30, 323 (1965).
10. F. Eisinger, J. Schreiber, and A. Eschenmoser, Helv. Chim. Acta., 43, 113 (1960).
11. F. C. Chang and N. F. Wood, Tetrahedron Letters, 2969 (1964).
12. I. R. Sherwood and W. F. Short, J. Chem. Soc., 1006 (1938); R. D. Haworth and B. P. Moore ibid., 633 (1946).
13. P. E. Sokol, Org. Syn., 44, 69 (1964).
14. P. A. Bartlett and W. S. Johnson, Tetrahedron Letters, 4459 (1970).
15. P. D. C. Dean, J. Chem. Soc., 6655 (1965).