

CROWN ETHER CATALYSIS: "NAKED" ANIONS AS
REACTIVE INTERMEDIATES IN THE SYNTHESIS OF PHENACYL ESTERS

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Since the time of their discovery, crown ethers have been shown to have a tremendous ability to complex metal salts, ^(1,2) especially those of potassium, and aid by solvation of the cation the dissolution of these salts in non-polar aprotic solvents. The reactive behavior of these salts in solution have shown unusual properties. The work of Sam and Simmons ⁽²⁾ allows the solution of potassium permanganate under the influence of dicyclohexyl-18-crown-6 ⁽³⁾ in solvents such as benzene where the permanganate anion acts as an efficient oxidizing agent. Sam and Simmons ⁽⁴⁾ have also observed that potassium halides and potassium hydroxide in benzene possesses strong nucleophilic and basic properties. The recent elegant observations of Liotta ⁽⁵⁾ on the reactivity of potassium fluoride and potassium acetate in non-polar aprotic solvents using 18-crown-6 ⁽³⁾ as the catalyst has shown that anions become extremely reactive in aprotic solution when their companion cations are complexed with crown ethers. Liotta also observed ⁽⁵⁾ that preliminary complexation of the salt with the crown ether is not necessary ⁽¹⁾ and that direct solution can be effected by this catalyst in aprotic solvents. This then allows the use of potassium halides as good nucleophiles in solvents not usually considered for such reactions.

The synthesis of phenacyl esters has many uses in organic chemistry. Hendrickson and Kandall ⁽⁶⁾ have reported using phenacyl esters of acids and phenols as protecting groups. Hendrickson reports that the use of phenacyl esters as protecting groups are especially attractive in that they are easily and selectively formed, stable to many reactive conditions used in organic synthesis, and released under very mild conditions. ⁽⁶⁾ Hendrickson reports that the phenacyl esters can be synthesized according to traditional methods ⁽⁷⁾ or by treating the sodium salt of the acid with the appropriate α -bromoacetophenone in DMF. The problems with the classical procedure are that slow reaction times, ⁽⁷⁾ hydrolysis of the alkylating agent, ⁽⁸⁾ low yields of product and contamination of products with starting alkylating reagent are observed. If the procedure is run in the presence of excess amounts of sodium chloride, anomalous results are sometimes obtained. ⁽⁹⁾

To circumvent the above problems we decided to run the reaction using the potassium salt of an acid and dicyclohexyl-18-crown-6 or 18-crown-6 as solubilizing catalyst. We found that doing this gave isolated yields of alkylated product of between 90-100%. The procedure could be used efficiently on either a small or large scale. It is especially valuable on a small scale reaction. The synthesis of phenacyl formates^(7,8) becomes quantitative in our system. Table One summarizes our results.

We find, as does Liotta,⁽⁵⁾ that either acetonitrile or benzene may be used as solvent, with the reaction proceeding faster in acetonitrile than in benzene. The usual reaction time is 10-30 minutes at reflux for acetonitrile, or several hours at room temperature, for quantitative formation of the derivative. The catalyst concentration was .05 molar in all reactions. We also observed that sodium salts could be used with the only penalty being longer reaction times. The following procedure is illustrative. Potassium acetate (100 mg, 1.02 mM), α , β -dibromoacetophenone (278 mg, 1.00 mM) and dicyclohexyl-18-crown-6 (15 mg, 0.04 mM) were suspended in 10 ml acetonitrile. The mixture was refluxed for 15 minutes at which time T.L.C. showed no starting bromide. The acetonitrile was removed under vacuum and the residue washed with benzene through a short column (4-5 g) of dry column silica gel. Removal of the benzene gave 252 mg of a white crystalline material, m.p. = 85-86° (lit. = 85°), yield = 98%. T.L.C. on silica gel showed only one spot, no catalyst eluting through the column. An alternate procedure in large scale runs is to recrystallize the crude product from benzene/hexane. The pure product is usually obtained in 75-90% yield after one recrystallization.

We believe that this new procedure offers many advantages over the classic procedure. Reaction time and conditions are short and extremely mild. Since the catalyst is used in such small concentrations, catalyst cost is not a factor in the reaction. The quantitative nature of the reaction, especially when dealing with small amounts of radioactive acids, may be used to derivatize very small amounts (1-2 mg) of potassium acid salts. The fact that there appears to be no steric problems with hindered acids coupled with the phenacyl esters usefulness as a protecting group leads us to believe that this procedure will be most useful in synthetic organic chemistry.

TABLE ONE

Acid	p-Bromophenacyl Derivative yield ^a	Derivative m.p. (lit.) ⁷
Formic Acid	93%	100.5-101.5° (101°)
Acetic Acid	98%	85-86° (85°)
Propionic Acid	98%	59-60° (59°)
Butyric Acid	97%	63-64° (63°)
Heptanoic Acid	99%	71-72° (72°)
Pivalic Acid	95%	77-78° (78°)
Benzoic Acid	93%	120-121° (119°)
2-Methylbenzoic Acid	90%	66-67° (57°)
2-Iodobenzoic Acid	92%	112-113° (110°)
Mesitoic Acid (2,4,6-trimethylbenzoic)	98%	98-99° ^b
4-t-Butylbenzoic Acid	92%	137-138° ^b

^a isolated yields

^b Previously unknown; identified by nmr and mass spectrum

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