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HYDROGEN BONDING IN ORGANIC SYNTHESIS V: POTASSIUM FLUORIDE IN CARBOXYLIC ACIDS AS AN ALTERNATIVE TO CROWN ETHER WITH ACID SALTS IN THE PREPARATION OF PHENACYL ESTERS

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The synthesis of phenacyl esters has many uses in organic chemistry. The majority of phenacyl esters are solids and as such, they provide a useful means for characterising acids or phenols. Hendrickson and Kandall have reported[1] the use of phenacyl esters as protecting groups in which they are especially attractive as they are stable to many reactive conditions used in organic synthesis and are released under very mild conditions such as treatment of the derivative with zinc in acetic acid[1]. Although phenacyl esters may be prepared according to traditional methods[2] or by treating the sodium salt of the acid with α-bormoacetophenone in D.M.F., there are several drawbacks to such procedures. The presence of alkalies in the reaction mixture causes hydrolysis of the phenacyl halides to phenacyl alcohols[2] or if the reactions are run in the presence of excess amounts of sodium chloride, anomalous results are sometimes obtained[3]. Furthermore, classical procedures are generally slow[2], provide low yields of product and contamination of products with starting materials is observed. Recently, Durst has overcome many of these problems by running the reaction using the potassium salt of an acid and dicyclohexyl-18-crown-6 as the solubizing catalyst under reflux conditions for 10-30 minutes[4].

Potassium fluoride is very soluble in glacial acetic acid[5] and indeed, in most other simple liquid carboxylic acids[6]. On dissolving KF in glacial acetic acid, a very strong hydrogen bond is formed between the fluoride anion and the acid hydroxyl oxygen[7,8]. This H-bond directs electrons from the electron rich fluoride anion to the organic part of the complex[9], thereby reducing the nucleophilicity of the acetoxy part of the complex[10]. Solutions of KF in acetic acid and mixtures of KF with other protic organic compounds capable of behaving as H-bond electron acceptors have provided extremely efficient routes to organic acetates[10] and to other organic condensation products[9,11,12].

We now wish to report a simple, inexpensive and efficient alternative to previous methods for the preparation of phenacyl esters. Treatment of α-bromoacetophenone with the carboxylic acid in the presence of KF provides quantitative formation of the derivative. For the majority of the carboxylic acids investigated, the conversion appears to go quantitatively at room temperature in ten minutes or less with D.M.F. as solvent. The exceptions to this are the sterically hindered 2,4,6-trimethylbenzoic and 4-t-butylbenzoic acids which require somewhat longer periods of reaction at room temperature and palmitic acid which only undergoes very slow reaction at room temperature. In such cases, the reaction time may be reduced to about ten minutes or less on heating the mixture to about 100°C. A mixture of KF with an aromatic or low molecular weight aliphatic carboxylic acid in D.M.F. often becomes warm on shaking as a result of the formation of a very strong H-bond between the fluoride anion and the acid hydroxyl oxygen--this may well be sufficient heat to drive the reaction to completion. Indeed, should the reactants be added in such a manner that the heat of the H-bond can dissipate before the α-bromoacetophenone is added, reaction at room temperature often requires a considerably longer period of time.

An alternative procedure to that involving D.M.F. as solvent is available for liquid carboxylic acids. In these cases, no solvent is necessary, an excess of the acid being used as the reaction medium and the reaction was found to proceed quantitatively at reflux temperatures in less than ten minutes. Replacing KF by caesium fluoride reduced the time of reaction somewhat and allowed the use of lower reaction temperatures[14], but we feel the disadvantages of this alternative due to the prohibitive cost of caesium fluoride outweighs the advantages.

Potassium fluoride (1.28 g, 0.022 mol)[15] and α-bromoacetophenone (1.99 g, 0.01 mol) were stirred together in N,N-dimethylformamide (10 g) at room temperature for one minute. Benzoic acid (1.22 g, 0.01 mol) was then added to the reaction mixture and the whole stirred at room temperature for ten minutes at which time ^{1}H n.m.r. showed no starting bromide. The product was extracted from the reaction mixture with diethyl ether, the ethereal extracts washed three times with equal volumes of water to remove the D.M.F.[16], dried and evaporated to give a white crystalline material, m.p. 117-18°C (lit.[17] 119-20°C), yield = 98%. In order to test the effect of moisture on these reactions, the above reaction was run in the presence of a little water (0.036 g, 0.002 mol). ^{1}H n.m.r. analysis showed 100% conversion to the ester after about 15 minutes. Separation gave the product in 96% yield, no detectable amounts of alcohol were found in the reaction mixture. A typical procedure for a liquid carboxylic acid where excess of the acid is used as solvent is to reflux a solution of KF (1.28 g, 0.022 mol) in glacial acetic acid (10 g) with α-bromoacetophenone (1.99 g, 0.01 mol). After 10 minutes, sampling and ^{1}H n.m.r. analysis showed no starting bromide. The product was extracted with diethyl ether, the ethereal extracts washed with bicarbonate, then water, dried and evaporated to give the crystalline ester, m.p. 50°C (lit.[17] 51-2°C), yield = 98%. Alternatively, where excess acid is used the reaction mixture may be separated by addition of excess KF to provide the stable monosolvate KF·HOAc which may be washed with diethyl ether to remove the product without removal of any unreacted acid. The crude products may be recrystallised from benzene/hexane or ethanol. The pure products are usually obtained in 80-90% yield after one recrystallisation.

We believe that this new approach to the synthesis of phenacyl esters offers many advantages over classical procedures and is a practical alternative to methods involving carboxylic acid salts. Our method does not require the use of alkali at any stage of the reaction and provides high yields of products in short periods of time and can usually be accomplished under mild conditions. The reactions involving the aromatic and low molecular weight aliphatic carboxylic acids described here are particularly attractive as they can be accomplished at room temperature with only a 10 mole% excess of KF[15] and no excess of acid required. Furthermore, there seem to be no serious steric problems when using hindered acids. Previous methods for the synthesis of phenacyl esters using carboxylic acid salts[1,4] usually require reaction times in excess of one hour at room temperature or 10-30 minutes at elevated temperatures.

TABLE I

Acid	Solvent	Temperature	Time[a]	Phenacyl ester Yield (%)[b]	Derivative m.p.(lit)°C
Acetic	D.M.F.	25°C	10	98	50(51-2[17])
	--	reflux	10	98	
Propanoic	D.M.F.	25°C	10	95	26
	--	reflux	10	93	
Trimethylacetic	D.M.F.	25°C	10	95	61(61-2[17])
	--	100°C	10	91	
Palmitic	D.M.F.	100°C	10	96	49(52[18])
Benzoic	D.M.F.	25°C	10	98	117-18 (119-20[17])
2-Methoxybenzoic	D.M.F.	25°C	3	99	62
4-t-Butylbenzoic	D.M.F.	25°C	60	99	71
	D.M.F.	100°C	10	97	
2,4,6-Trimethylbenzoic	D.M.F.	25°C	20	96	80(80-1[19])

[a] Reaction time after which ^1H n.m.r. analysis shows no starting bromide

[b] Isolated yields

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13. An alternative procedure to running the reactions involving solid acids in D.M.F. is to simply use the melted acid as the solvent, this procedure is as effective although it is, of course, only suitable for acids with reasonably low melting points.
14. For the aliphatic carboxylic acids using excess acid as solvent, all reactions were found to go to completion within one hour on warming to about 90°C. Replacing KF by caesium fluoride allowed steady reaction at 60°C instead of 90°C.
15. For the reaction: $2KF + RCO_2H + R'COCH_2Br \longrightarrow R'COCH_2O_2CR + KBr + KHF_2$, it can be seen that a minimum 100 mole% excess of KF relative to the other reactants is required. In practice, the mole ratio of the above reactants actually used is 2.2:1:1 respectively.
16. This was found to be a completely effective process for removing all detectable traces of D.M.F.
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