

An Efficient Acetylation of Primary and Secondary Aliphatic Alcohols with Acetic Anhydride in the Presence of Graphite Bisulphate

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In cyclohexane, thirteen examples of primary and secondary aliphatic alcohols were easily converted to the corresponding acetate derivatives within a short time, ranging from 5 min to 2.5 h, and in good yields close to 90 %, using acetic anhydride as reagent and graphite bisulphate as an efficient catalyst.

Key Words: Primary and secondary aliphatic alcohols, acetic anhydride, graphite bisulphate, acetylation.

Introduction

Alcoholic hydroxy groups are common functional groups in organic compounds. Hydroxy compounds are often converted to acetate derivatives for protection or characterization of the structure. For this purpose, acetic anhydride is commonly employed¹ with an acid or base catalyst, such as zinc chloride, concentrated sulphuric acid, anhydrous sodium acetate or, most often, pyridine^{2a}.

Although many reactions are conveniently carried out in homogeneous solutions, with or without solvent, reactions occurring between two phases can present several advantages. Solid phase synthesis³ utilises reactive residues attached to insoluble polymeric supports as reagents in synthesis. The main advantages of solid phase synthesis are the ease of the separation of products and selectivity⁴ in some cases. The use of graphite instead of a polymer to insolubilize a reagent offers still other interesting prospects. Many graphite insertion compounds⁵ have been synthesized and used in organic synthesis⁶. Of the graphite insertion compounds the one with sulphuric acid (graphite bisulphate) is to be of interest in organic chemistry because sulphuric acid has many catalytic properties. Graphite bisulphate has the formula $C_{24}^+HSO_4^-.2H_2SO_4$, and is easily handled by electrolysis^{6a} of conc. sulphuric acid by graphite anode or chemical oxidation⁷ of crystalline graphite. Graphite bisulphate has been used in many organic synthesis as an efficient catalyst: in the formation of many ketals^{7a}, the isomerization of butenes⁸ and the isomerization of trimethylbenzenes⁹. Kagan¹⁰ and co-workers investigated the use of graphite bisulphate in esterification with surprisingly good results. They worked in cyclohexane at room temperature with equimolar amounts of alcohol and carboxylic acid, and at the end of the reaction, isolated ester after the filtering off of the

graphite bisulphate and evaporation of the solvent. In this way, yields close to 90 % were obtained within 1-20 h according to the structure of the reactant. While primary alcohols or benzylic alcohols are rapidly esterified, secondary alcohols are esterified more slowly. Even many dicarboxylic acids are esterified, the insoluble starting material being progressively dissolved as ester is formed. By following the study of Kagan and co-workers, we applied this method to acetylation of primary and secondary alcohols through using acetic anhydride instead of acid. We here report our results obtained by acetylation of aliphatic alcohol examples.

Experimental Section

The Preparation of Graphite Bisulphate^{7a}: 5 g of Crystalline Graphite (300-mesh) and 3.5 ml HNO₃ (d=1.49 g/ml) are added to 50 ml of H₂SO₄ (d=1.84 g/ml). The mixture is stirred magnetically for 48 h at room temperature. At the end of stirring, the deep blue colour of graphite bisulphate is seen. The mixture is poured to a centrifuge tube and centrifuged at 7,000 rpm. After separation of sulphuric acid by decantation, graphite bisulphate is protected from water and then used.

General Procedure for the Acetylation of Alcohols: To a stirred solution of 10 mmol of alcohol in 30 ml of cyclohexane (carbon tetrachloride may be used) are added acetic anhydride equivalently (10 mmol for monohydroxy alcohol, 20 mmol for dihydroxy alcohol, 30 mmol for trihydroxy alcohol) and 350 mg of graphite bisulphate (0.6 mmol). The mixture is magnetically stirred at room temperature and reaction is monitored by ¹H-NMR spectrum. After completion of acetylation, the solution is decanted, neutralised by solid NaHCO₃, and then filtered. Evaporation of the solvent gives the corresponding acetate derivative.

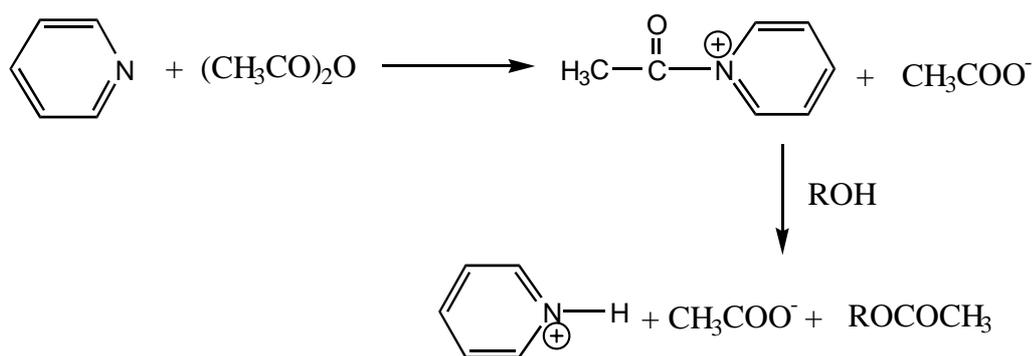
Results and Discussion

Either graphite bisulphate catalysed acetylations or those performed in pyridine were monitored by ¹H-NMR spectra to determine the reaction time exactly. The structures of all acetate derivatives were determined by comparison of their ¹H-NMR spectra with authentic samples. As seen at Table 1, graphite bisulphate catalysed acetylation occurs very fast and yields are higher than with acetylation in pyridine.

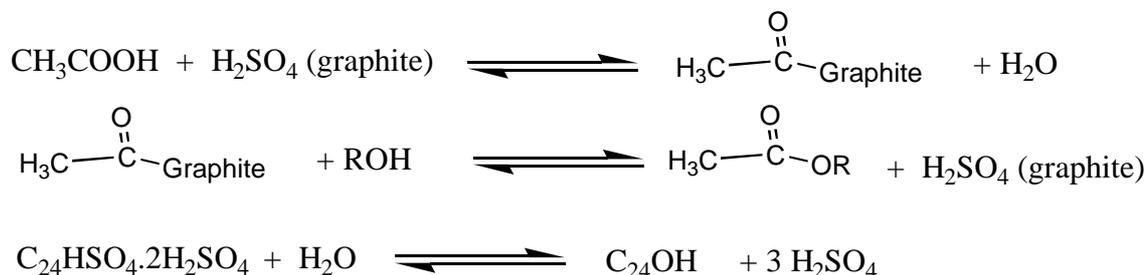
Table 1. Acetylation of alcohols with acetic anhydride in cyclohexane using graphite bisulphate as catalyst

Acetylated alcohol	Product	Reaction Time	Yield %
Benzyl alcohol	Benzylacetate	5 min	93
2-Ethoxyethanol	2-Ethoxyethylacetate	15 min	91
n-Butanol	n-butylacetate	20 min	88
iso-Amyl alcohol	iso-Amylacetate	20 min	96
Allyl alcohol	Allyl acetate	20 min	94
Cyclohexanol	Cyclohexylacetate	20 min	95
(-)-Menthol	(-)-Menthylacetate	20 min	91
Glycerol	1,2,3-Triacetoxyp propane	20 min	92
trans-1,2-Cyclohexanediol	trans-1,2-Diacetoxycyclohexane	20 min	94
trans-1,2-Cyclopentenediol	trans-1,2-Diacetoxycyclopentane	30 min	82
cis-1,2-Cyclohexanediol	cis-1,2-Diacetoxycyclohexane	30 min	92
n-Octadecanol	n-Octadecylacetate	1.5 h	87
iso-Propanol	iso-Propylacetate	2.5 h	87

The times of acetylation of the alcohols used with acetic anhydride in pyridine were much longer and yields were some what lower; (n-butanol (8 h, 73 %), iso-amyl alcohol (8 h, 77 %), glycerol (7 h, 74 %), trans-1,2-cyclohexanediol (7 h, 84 %), n-octadecanol (26 h, 72 %), iso-propanol (26 h, 74 %)) The question remains of why both n-octadecanol and iso-propanol acetylate so slowly, by pyridine or graphite bisulphate catalyst in comparison with the others. In the literature, it is reported that in both reactions, first an acetyl-pyridine^{2b} or acyl-graphite^{6a} intermediate formed. Alcohol then attacks the formed intermediate as a nucleophile. For this reason, it is readily understood that nucleophilic attacks of these alcohols occur slowly, probably due to steric factors.(Scheme-1 and 2).



Scheme-1^{2b} Acetylation mechanism of alcohols with Ac₂O in pyridine



Scheme-2^{6a} Mechanism of esterification in the presence of graphite bisulphate

Additionally, the use of the physical mixture of graphite and sulphuric acid instead of graphite bisulphate does not have the same effect. For example, the acetylation of cyclohexanol by the physical mixture of graphite and sulphuric acid ended within 3.5 h with a yield of 91 %. The acetylation of n-butanol resulted within 4h and with a yield of 85 %.

The reaction time of acetylation of secondary alcohols is noteworthy: while acetic acid and cyclohexanol converted to cyclohexyl acetate in 17h¹⁰ in the presence of graphite bisulphate, with the substitution of acetic anhydride for acetic acid the same conversion occurred in only 20 minutes. With the esterification mechanism shown in scheme 2, these results can be easily explained. The first step of esterification is the formation of acyl-graphite by the leaving of the hydroxy (OH) group after protonation. In the use of acetic anhydride, this step will result in the leaving of the acetic acid (CH₃COOH) molecule. Although both hydroxide and acetate are leaving after protonation, one may readily estimate the leaving of acetate is easier than the leaving of the hydroxide group, considering base strength.

Another issue is the solvent effect. Graphite salts are instantly decomposed by water and by polar organic solvents^{5a}. For this reason, in some of our experiments, we used carbon tetrachloride as a nonpolar and cheaper solvent, and it was seen that the reaction rates were fast and the yields were as high as those cyclohexane.

In conclusion, it can be seen that the most significant role of graphite bisulphate is to expedite the acetylation reactions. In our method, purification is easily accomplished by the filtering off graphite bisulphate, followed by the neutralisation of the excess acid. The ease of purification of the formed acetate, and the good yields occurring with the reactions can be acceptable as additional advantages.

Our studies on acetylation of phenols, tertiary alcohols and polyhydroxylated systems are currently in progress.

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