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AN EFFICIENT AND SIMPLE PROCEDURE FOR PREPARATION OF ESTERS AND ANHYDRIDES FROM ACID CHLORIDES IN THE PRESENCE OF 1,4-DIAZABICYCLO[2.2.2]OCTANE (DABCO) UNDER SOLVENT-FREE CONDITIONS

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ABSTRACT

A manipulatively one-pot and rapid method for the synthesis of aliphatic and aromatic ester and anhydride from acid chloride and alcohol or potassium salt of carboxylic acid under solvent-free conditions is reported. The reaction has been carried out in excellent yield and short reaction time in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) under solvent-free conditions.

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The protection of hydroxyl group of alcohols and phenols by formation of esters is of great importance in synthetic organic chemistry.¹ Although several methods employ transesterification method,² the esterification of alcohols and phenols is routinely carried out by acid anhydride or acid chloride in the presence of tertiary amines such as triethylamine and pyridine.³ 4-(Dimethylamino)pyridine(DMAP) as a much more efficient catalyst for acylation of tertiary alcohols is particularly noteworthy.⁴ Tributylphosphine has been used as a similar catalyst for protection of alcohols.⁵ Recently, iodine was reported to be a useful catalyst for esterification of alcohols.⁶ In addition to the above catalysts, protonic acid such as *p*-toluenesulfonic acid,⁷ Lewis acids such as zinc chloride,⁸ cobalt chloride⁹ and scandium trifluromethansulfonate¹⁰ were also applied to catalyze the protection of alcohols and phenols. More recently chlorotrimethylsilane,¹¹ lithium chloride¹² and ferric perchlorate¹³ have been used for acetylation of alcohols. Each of the above methods has its merit and some shortcomings. There is still a great demand for acid catalysts to generate esters under mild conditions and environmentally friendly process. Monmorillonite K-10 and KSF¹⁴ were applied as solid catalysts for protection of hydroxyl group of alcohols and phenols to obtain relatively better results.

Heterogeneous reaction that are facilitated by supported reagents on various solid inorganic surfaces have received attention in recent years.^{15–17} The advantage of these methods over conventional homogenous reactions is that they provide greater selectivity, enhanced reaction rates, cleaner products and manipulative simplicity. In connection with our ongoing program to develop environmentally benign methods using solid supports,¹⁸ herein we wish to report an extremely convenient method for esterification of different acid chloride with different alcohols and phenols in the presence of DABCO under solvent-free conditions (Scheme 1).



The process in its entirety involves a simple mixing of acid chloride and alcohols in the presence of DABCO in a mortar and grinding the mixture for the time specified in the Table 1 at room temperature. Copyright @ Marcel Dekker, Inc. All rights reserved.



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ESTERS AND ANHYDRIDES FROM ACID CHLORIDES

Table 1. Preparation of Esters

| Entry | R ₁ | R ₂ | Reaction Time (min) | Yield (%) ^a | bp/mmHg or M.P. $^{\circ}$ C (Lit.) $^{2-14}$ |
|-------|---------------------------------|------------------------------------|------------------------|---------------------------|---|
| 1 | CH ₃ | CH ₃ | 2 | 92 | 75/760 (75) |
| 2 | CH ₃ | CH ₃ CH ₂ | 4 | 95 | 179-183/760 (179-181) |
| 3 | CH ₃ | $CH_3(CH_2)_2$ | 4 | 95 | 126-128/760 (126-127) |
| 4 | CH ₃ | C_6H_5 | 8 | 97 | 93-95/20 (196/760) |
| 5 | CH ₃ | 4-MeOC ₆ H ₄ | 5 | 95 | 31-32 (32) |
| 6 | CH ₃ | $2-NO_2C_6H_4$ | 10 | 90 | 39-40 (40-41) |
| 7 | CH ₃ | cyclohexyl | 6 | 90 | 173/760 (172) |
| 8 | CH ₃ | s-butyl | 5 | 95 | 114/760 (112) |
| 9 | CH ₃ | 1-naphthyl | 10 | 89 | 46-47 (47-48) |
| 10 | CH ₃ CH ₂ | CH_3CH_2 | 4 | 95 | 98/760 (98) |
| 11 | $CH_3(CH_2)_8$ | CH_3CH_2 | 6 | 85 | 245/760 (242) |
| 12 | C ₆ H ₅ | CH ₃ | 8 | 98 | 197-198/760 (199) |
| 13 | C_6H_5 | (CH ₃) ₂ CH | 8 | 90 | 265-267/760 (262) |
| 14 | C_6H_5 | C_6H_5 | 10 | 95 | 67-69 (68-70) |
| 15 | $4-BrC_6H_4$ | CH ₃ | 10 | 93 | 80 (81) |
| 16 | $4-NO_2C_6H_4$ | CH ₃ | 10 | 94 | 95 (96) |
| 17 | $4-NO_2C_6H_4$ | CH ₃ CH ₂ | 10 | 98 | 55 (57) |
| 18 | $3-NO_2C_6H_4$ | CH_3CH_2 | 10 | 98 | 49 (47) |
| 19 | $4-NO_2C_6H_4$ | CH ₃ | 10 | 92 | 59 (79) |

^aIsolated yield after simple extraction.

To the best of our knowledge this methodology for preparation of esters under solid phase conditions has not been reported in literature. This method is very fast and purification of product is very easy (Scheme 1).

The esters have been identified by ¹H NMR analyze by comparing with authentic compounds the results of these efforts are presented in Table 1. the desired product was usually isolated in excellent yield (Table 1). As shown in Table 1, a series of acid chlorides were reacted with alcohols and phenols in the presence of DABCO under solvent-free conditions. Primary and secondary alcohols and phenol could be easily reacted with different acid chlorides at room temperature. No selective esterification between primary, secondary alcohol and phenol was observed. The tertiary alcohols remained unchanged even the reaction mixture was heated at 70°C for 2 h. These results indicated that DABCO was not efficient reagent for esterification of tertiary alcohols. It is noteworthy that DABCO could recovered easily by filtration and washing with NaOH 10% and extraction with CH₂Cl₂ and could be reused again without significant decrease in its activity.



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Acid anhydrides are among the most important class of reagents used in organic synthesis. They are the preferred reactive acid derivatives for the preparation of amides, esters and peptides.¹⁹ Further, the use of acid anhydrides does not require any acid scavengers unlike in the case of acid chloride.

We also have used this method for the synthesis of various symmetrical and unsymmetrical anhydrides. This method involves the reaction of potassium salt of various carboxylic acids with different acid chlorides in the presence of DABCO at room temperature under solvent-free conditions (Scheme 2 and Table 2). The potassium salts were prepared by dissolving the respective carboxylic acids in methanol at room temperature (rt.), adding



Scheme 2.

| Entry | R ₁ | R ₂ | Reaction Time (min) | Yield (%) ^a | M.P. °C (Lit.) ^{20–25} |
|-------|--|---|------------------------|---------------------------|------------------------------------|
| 1 | C ₆ H ₅ | C ₆ H ₅ | 6 | 98 | 43 (42–43) |
| 2 | p-ClC ₆ H ₄ | p-ClC ₆ H ₄ | 7 | 98 | 195–96 (195) |
| 3 | p-MeC ₆ H ₄ | <i>p</i> -MeC ₆ H ₄ | 5 | 96 | 94-95 (95) |
| 4 | $p-NO_2C_6H_4$ | p-NO ₂ C ₆ H ₄ | 8 | 93 | 188-190 (189) |
| 5 | <i>m</i> -MeOC ₆ H ₄ | <i>m</i> -MeOC ₆ H ₄ | 5 | 99 | 65-67 (67) |
| 6 | C ₆ H ₅ | $p-ClC_6H_4$ | 6 | 94 | 73-75 (68-70) |
| 7 | $p-ClC_6H_4$ | C ₆ H ₅ | 6 | 90 | 73-75 (68-70) |
| 8 | C_6H_5 | $p-NO_2C_6H_4$ | 8 | 99 | 136-138 (131) |
| 9 | $p-NO_2C_6H_4$ | C_6H_5 | 5 | 99 | 136-138 (131) |
| 10 | CH ₃ | $p-ClC_6H_4$ | 7 | 95 | 197-98 (196-97) |
| 11 | $p-ClC_6H_4$ | CH ₃ | 6 | 98 | 197-98 (196-97) |
| 12 | CH ₃ | p-MeC ₆ H ₄ | 8 | 96 | 94-95 (94-95) |
| 13 | p-MeC ₆ H ₄ | CH ₃ | 10 | 92 | 94-95 (94-95) |
| 14 | CH ₃ | $p-NO_2C_6H_4$ | 6 | 97 | 184-85 (183-85) |
| 15 | $p-NO_2C_6H_4$ | CH ₃ | 4 | 99 | 184-85 (183-85) |
| 16 | <i>m</i> -MeOC ₆ H ₄ | CH_3 | 10 | 94 | 65-67 (63-66) |
| 17 | CH ₃ | m-MeOC ₆ H ₄ | 10 | 98 | 65-67 (63-66) |

^aIsolated yield after simple extraction.



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ESTERS AND ANHYDRIDES FROM ACID CHLORIDES

methanolic-KOH (1:1) to the reaction mixture and stirring the reaction mixture at rt. for 30 min. followed by filtration. This is a rapid and very convenient method for the synthesis of both symmetric as well as unsymmetrical acid anhydrides in excellent yields with high purity. By this method a variety of acid anhydrides such as aliphatic–aromatic, aliphatic– aliphatic and aromatic–aliphatic acid anhydride types can be readily prepared in short reaction time at room temperature under solvent-free conditions (Table 2).

We believe that the effect of DABCO is to react with acid chloride to produce 1-aza-acyl-4-azoniabycyclo[2.2.2]ocatane chloride. This salt then reacts with alcohol or potassium salt of carboxylic acid to produce corresponding ester or anhydride, the probably mechanism is shown in Scheme 3.



Scheme 3.

The Structure of intermediate (i.e. 1-aza-*p*-nitrobenzyl-4-azoniabicyclo[2.2.2]ocatane chloride that obtained in this work showed two very strong and sharp bands in the region $1800-1715 \text{ cm}^{-1}$ due to symmetric and asymmetric carbonyl stretching vibrations, characteristic of this intermediate.

In conclusion a simple and efficient method for synthesis of esters and acid anhydrides under solvent-free conditions at room temperature has been developed. This method should allow a more rapid and complete screening of substituent effects on protection of alcohols than the method which has previously been reported. This work also is a rapid and very convenient method for the synthesis of both symmetric as well as unsymmetric acid anhydride in excellent yields with high purity. By this method a variety of acid anhydrides such as aliphatic–aromatic, aliphatic–aliphatic and aromatic–aliphatic acid anhydride type can be readily prepared in short reaction time. This methodology is superior from point of view of yield, short reaction time and the easier work-up than the reported methods.

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EXPERIMENTAL

General

All products were identified by spectroscopic data (IR, NMR) and melting or boiling point by comparing with authentic compounds.^{2–14,20–25} The structure of all the anhydrides that obtained in this work showed two very strong and sharp absorption bands in the region $1800-1720 \text{ cm}^{-1}$, due to symmetric and asymmetric carbonyl stretching vibrations, characteristic of acid anhydrides. All mps. were taken on a Gallenkamp melting apparatus and are uncorrected. ¹H NMR spectra were recorded on a Varian EM-390 NMR Spectrometer operating at 90 MHz. The spectra were measured in CCl₄ and CDCl₃ relative to TMS (0.00 ppm). IR spectra were recorded on a Shimadzu 435 IR spectrophotometer. Spectra of solids were performed using KBr pellets.

General Procedure

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After a mortar was charged with acid chloride (1 mmol), DABCO (0.11 g, 1 mmol), the mixture was ground with a pestle for 1 min until the reaction mixture solidified. Then alcohol (1 mmol) or potassium salts of carboxylic acid (1 mmol) was added to the mixture. The reaction mixture was ground for the time specified in Table 1 and 2. Then the reaction mixture was poured into a mixture of ether (20 ml) and H₂O (5 ml). The ethereal layer was dried (CaCl₂), and evaporated to dryness using a rotary evaporator to give the pure product.

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