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Simple Preparation of Symmetrical Carboxylic Acid Anhydrides by Means of $Na_2CO_3/SOCl_2$

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Abstract: A convenient and general method for the synthesis of symmetrical carboxylic acid anhydrides using sodium carbonate/thionyl chloride is described.

Keywords: carboxylic acid anhydride, simple preparation, sodium carbonate, symmetrical, thionyl chloride

Symmetrical carboxylic acid anhydrides have been recommended as reagents for esters, amides, and peptide synthesis.[1,2] Generally, carboxylic acid anhydrides are prepared by reacting sodium, potassium, and especially thallium salts of carboxylic acids with powerful acylating agents, such as acid chlorides[3,4] or acid anhydrides,[3,5] or reacting carboxylic acids with dehydrative coupling agents such as thionyl chloride,[2] ketene,[6] phosgene,[7] dicyclohexylcarbodiimide,[8] N,N-carbonyldimidazole,[6] isocyanate,[9] ethoxyacetylene,[6] bromotriphenylphosphonium bromide,[10] N-phenylphosphoramidochloridate,[10] diphenylphosphorochloridate,[10] bis (trichloromethyl) carbonate,[7] or trichloroacetonitrile/PPh_3.[3] However, many of these methods have some limitations, including low yields, laborious procedures, expensive or not readily accessible reagents, unstable or special reagents, harsh reaction conditions,

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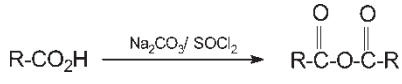
necessary presence of a phase-transfer catalyst, or perhaps, most importantly, tedious workup. Therefore, introducing mild, efficient, and inexpensive reagents and methods for such functional group transformation still is in demand. In our development of new methods for functional group transformation,[11] we are especially interested in developing the application of a modified form of thionyl chloride in organic synthesis. Along this line, very recently we have found that $SOCl_2$ in the presence of polyvinylpyrrolidone,[11e] 1,4-diazabicyclo[2.2.2]octane,[11f] and Na_2SO_3[11g] serves as a mild dehydrating agent for the conversion of aldoximes to the corresponding nitriles. Here we report a facile method for dehydration coupling of carboxylic acids to their corresponding symmetrical anhydride by use of sodium carbonate/thionyl chloride as efficient dehydrative coupling reagent under mild nonaqueous reaction conditions (Scheme 1).



Scheme 1.

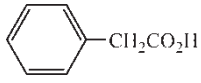
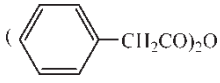
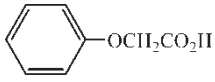
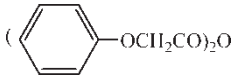
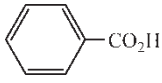
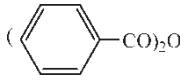
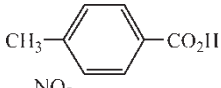
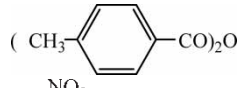
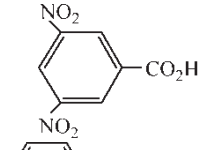
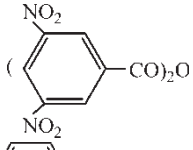
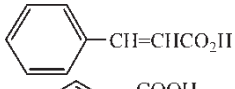
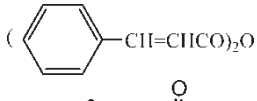
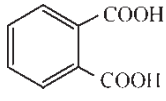
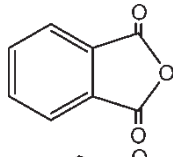
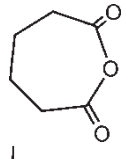
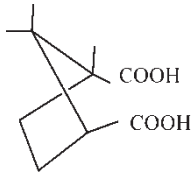
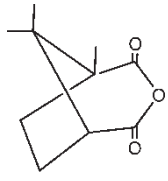
The reagent was easily prepared by the reaction of thionyl chloride with a stoichiometric amount of sodium carbonate at 0°C. Several controlled reactions were carried out to establish the optimal reaction conditions and revealed that simple stirring of benzoic acid (1 equivalent) and 1 equivalent of $Na_2CO_3/SOCl_2$ (1:1) in a 1:1 mixture of CH_2Cl_2/dioxane under reflux conditions effected the formation of benzoic anhydride in 88% isolated yield within 2.5 h. However, the same reaction in CH_2Cl_2 or dioxane afforded benzoic anhydride product in 42% or 50%, respectively, along with unreacted benzoic acid, even after longer reaction time periods. The effects of other solvents such as CCl_4, CH_3CN, and tetrahydrofuran (THF) were also studied, but in comparison with a 1:1 mixture of CH_2Cl_2/dioxane, the reaction times were longer and the yields were considerably lower.

The scope and generality of this process is illustrated with several examples, and the results are summarized in Table 1. The structure of all the products were settled from their analytical and spectral (IR, ^{1}H NMR) data and by direct comparison with authentic samples.

As shown in Table 1, the procedure turned out to be general for a range of structurally diverse carboxylic acids. Aliphatic and aromatic carboxylic acids were easily dehydrated and afforded the corresponding anhydrides in high isolated yields. It is noteworthy that no evidence for the formation of carboxylic acid chlorides as by-products of the reaction was observed. The yield of the reaction in the absence of Na_2CO_3 was very low.

Dicarboxylic acids under the same reaction conditions were cleanly, easily, and efficiently converted to the corresponding cyclic anhydride in high isolated yields. Even the sterically hindered camphoric acid has been

Table 1. . Conversion of carboxylic acids to anhydrides using Na_2CO_3/thionyl chloride

No.	Substrate	Product	Time (h)	Yield (%)
1	$CH_3(CH_2)_3CO_2H$	$(CH_3(CH_2)_3Co)_2O$	2	87
2	$CH_3(CH_2)_{16}CO_2H$	$(CH_3(CH_2)_{16}CO)_2O$	2	90
3			3	87
4			3	88
5			2.5	88
6			3	87
7			3	87
8			3	86
9			3	85
10	$HOOC(CH_2)_4COOH$		3	84
11			3.5	85

Molar ratio of substrate to reagent was 1:1 performed under reflux conditions.

Yields refer to be isolated products.

Products were characterized by comparison of their physical data, IR, and NMR spectra with those of known samples.

successfully converted to the corresponding cyclic anhydride, camphoric anhydride, in 86% isolated yield.

Compared to some previously reported reagents with major or minor drawbacks, several noteworthy features of this system are apparent. These are the easy workup procedure, availability of the reagent, operational simplicities, and use of inexpensive reagent.

In summary, we believe this procedure using $Na_2CO_3/SOCl_2$ will present a useful and convenient alternative to the existing methods for dehydration coupling of carboxylic acids. Further application of this dehydrative system in organic synthesis are currently under investigation.

EXPERIMENTAL

General

Sodium carbonate and thionyl chloride were purchased from Fluka Company. Carboxylic acids were purchased from Fluka and Merck. Products were characterized by comparison of their physical data and IR and ^1H NMR spectra with authentic samples. The purity determination of the products and reaction monitoring were accomplished by thin-layer chromatography (TLC) on silica-gel polygram SILG/UV 254 plates.

General Procedure for the Conversion of Carboxylic Acid to Carboxylic Acid Anhydrides with $Na_2CO_3/SOCl_2$

Fine powdered sodium carbonate (1 mmol, 0.106 g) was mixed with the freshly distilled thionyl chloride (1 mmol, 0.120 g) in a 25-ml, round-bottomed flask at room temperature. To the resulting powder, a solution of carboxylic acid (1 mmol) in a 1:1 mixture of anhydrous CH_2Cl_2/dioxane (5 ml) was slowly added and stirred under reflux conditions. The progress of the reaction was followed by TLC until no starting material could be detected. After cooling to ambient temperature, the product was then filtered and the residue washed thoroughly with CH_2Cl_2 (5 ml). Evaporation of solvent under reduced pressure furnished the desired anhydride in 43–90% isolated yields.

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