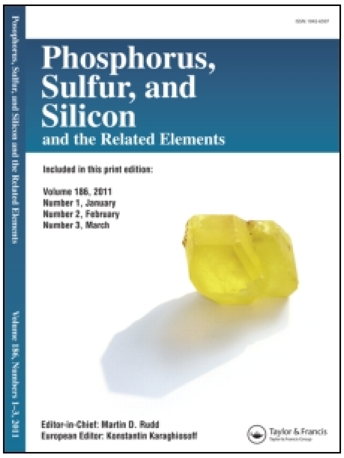

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$Na_2CO_3/SOCl_2$: A MILD AND CONVENIENT REAGENT FOR THE PREPARATION OF ISOPROPYL CARBOXYLATES

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$Na_2CO_3/SOCl_2$: A MILD AND CONVENIENT REAGENT FOR THE PREPARATION OF ISOPROPYL CARBOXYLATES

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$Na_2CO_3/SOCl_2$ has been used for esterification of aliphatic and aromatic acids with isopropanol. This esterification method is compatible with a wide assortment of functional groups.

Keywords: Esterification; isopropyl carboxylate; isopropyl ester; sodium carbonate; thionyl chloride

Esterification is an important and well-established reaction that is widely used in organic synthesis for various purposes.[1–2] A wide variety of esterification methods for carboxylic acids have been reported.[2,3] Most of the commonly used methods are either reaction of carboxylic acids with alkyl halides under basic conditions or condensation of carboxylic acids with alcohols under acidic conditions.[2] In addition to homogeneous acids (sulphuric acid, hydrogen chloride, orthophosphoric acid, and boric acid), metal salts supported on solid supports are well known as catalysts for condensation of carboxylic acids with alcohols.[4] Other methods also have been suggested recently.[5] The disadvantages of using these catalysts include long reaction time, low yield, expensive reagents, and tedious operation, and are difficult to avoid. Hence, a need still exists for a convenient, simple, and facile procedure to prepare esters under mild conditions and using readily available reagents.

In continuation of our efforts to explore new methods for functional group transformation,[6] we are especially interested in developing the application of a modified form of thionyl chloride in organic synthesis. Along this line, very recently we found that $SOCl_2$ in the presence of

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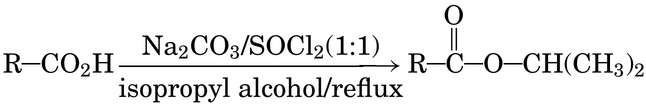
polyvinylpyrrolidone,[6e] 1,4-diazabicyclo[2.2.2]octane,[6f] and Na_2SO_3[6g] serve as mild dehydrating agents. In view of the great utility of esters as valuable intermediates in chemical and pharmaceutical industries,[1] it may be worthwhile to explore the versatility of thionyl chloride in esterification reaction. In 1996, a report by Hosangadi et al.[7] outlined the esterification of aromatic carboxylic acids with some primary alcohols such as methanol, ethanol, and n-butanol. Here we describe results that successfully led to the development of a novel, simple method for the esterification of aliphatic and aromatic carboxylic acids with isopropanol using sodium carbonate/thionyl chloride under mild reaction conditions.



$$R{-}CO_2H \xrightarrow[\text{isopropyl alcohol/reflux}]{Na_2CO_3/SOCl_2(1:1)} R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}CH(CH_3)_2$$

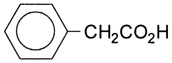
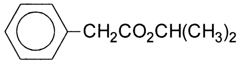
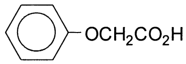
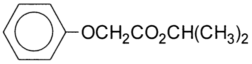
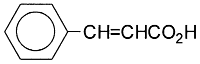
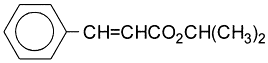
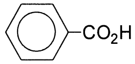
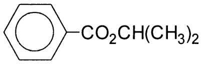
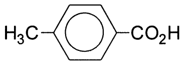
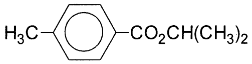
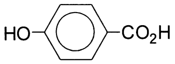
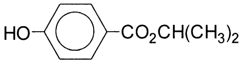
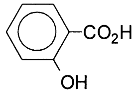
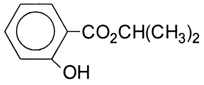
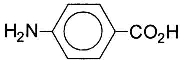
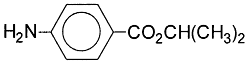
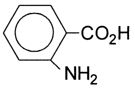
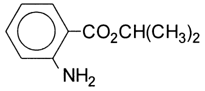
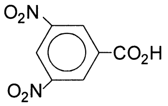
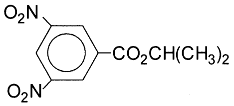
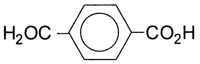
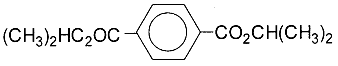
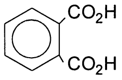
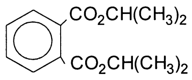
The reagent was easily prepared by the reaction of thionyl chloride with stiochiometric amount of sodium carbonate at room temperature. Initially, in order to establish the optimal reaction conditions, conversion of benzoic acid to isopropyl benzoate was studied. In order to achieve a high conversion of the starting carboxylic acid (1 equiv.) in reasonable time, application of isopropyl alcohol as solvent, reflux conditions and one equivalent of $Na_2CO_3/SOCl_2$ were required. Similar transformations with different starting carboxylic acid in isopropyl alcohol were carried out. In all cases, the reaction led to a single product and the products were obtained in pure form after aqueous basic work-up without further purification.

The scope and generality of this process is illustrated with several examples and the results are summarized in Table I Aliphatic and aromatic carboxylic acids were easily converted to the corresponding isopropyl ester in moderate to high yields. As shown in Table I the yield of esterification reaction was markedly lowered by introducing strong electron-donating groups such as hydroxyl or amino groups in ortho position of the aromatic ring. The structure of all the products were characterized from their analytical and spectral (IR, ^1H NMR) data and by direct comparison with authentic samples.

The tolerance of various functional groups under the present reaction conditions has been examined by reacting the substrates bearing OPh, OH, NO_2, NH_2, and olefinic groups. It was found that the yield of reaction in the absence of Na_2CO_3 was very low.

Dicarboxylic acids under the same reaction conditions and with two equivalents of $Na_2CO_3/SOCl_2$ were cleanly, easily, and efficiently converted to the corresponding diisopropyl ester in high isolated yields.

TABLE I Conversion of Carboxylic Acids to Isopropyl Ester Using Na_2CO_3/ Thionyl Chloride[a,b]

Entry	Substrate	Product	Yield%[c,d]
1	$CH_3(CH_2)_{16}CO_2H$	$CH_3(CH_2)_{16}CO_2CH(CH_3)_2$	89
2			89
3			88
4			91
5	$HO_2C(CH_2)_4CO_2H$	$(CH_3)_2HCO_2C(CH_2)_4CO_2CH(CH_3)_2$	89
6	$HO_2C(CH_2)_2CO_2H$	$(CH_3)_2HCO_2C(CH_2)_2CO_2CH(CH_3)_2$	90
7	$HO_2CCH{=}CHCO_2H$	$(CH_3)_2HCO_2CCH{=}CHCO_2CH(CH_3)_2$	91
8	$HO_2CCH(OH)CH(OH)CO_2H$	$(CH_3)_2HCO_2CCH(OH)CH(OH)CO_2CH(CH_3)_2$	92
9			89
10			90
11			90
12			22
13			89
14			37
15			83
16			89
17			87

[a] Molar ratio of substrate to reagent for mono carboxylic acids was 1:1 and for dicarboxylic acids was 1:2.

[b] Reactions performed under reflux conditions for 2h.

[c] Yields refer to pure isolated products.

[d] Products were characterized by comparsion of their physicial data, IR, NMR spectra with known samples.

Compared to some previously reported reagents with major or minor drawbacks, several noteworthy features of this system are apparent. These are: the easy work-up 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 esterification reaction.

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, IR and ^1H NMR spectra with authentic samples. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates.

General Procedure for the Conversion of Carboxylic Acid to Isopropyl Ester 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 isopropyl alcohol (5 ml) was slowly added and stirred under reflux conditions for 2 h. On completion of the reaction, the reaction mixture was poured into dilute solution of $NaHCO_3$ (10%) until the pH of the reaction mixture reached 9 and extracted with CH_2Cl_2 (15 ml). The organic layer was dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure to afford the TLC and ^{1}HNMR pure products in 22–92% isolated yields.

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