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Facile Esterification of Sulfonic Acids and Carboxylic Acids with Triethylorthoacetate[1]

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Abstract: *Triethylorthoacetate was found to be surprisingly more effective than triethylorthoformate in the esterification of sulfonic acids and carboxylic acids. Using this reagent, esters of sulfonic and carboxylic acids are prepared in high yields.*

The use of orthoesters, particularly triethylorthoformate (TEOF) for the conversion of carbonyl compounds to their acetals is well documented.[2] Various catalysts including ammonium chloride, ferric chloride, ammonium nitrate, and acidic ion exchange resins have been used for this transformation. Recently we attempted the protection of an aldehyde in our laboratories using triethylorthoacetate (TEOA) in the presence of pyridinium p-toluenesulfonate as the catalyst. To our surprise in addition to some of the desired acetal, ethyl p-toluenesulfonate was isolated as a product. This led us to investigate the relative reactivity of TEOA and TEOF in esterification reactions. In this paper we would like to report the results of our study that show TEOA is a convenient and cheap reagent for the facile esterification of sulfonic and carboxylic acids.

Numerous methods are known for the preparation of esters of carboxylic acids.[3] In particular, it is known that carboxylic acids are converted into their esters when heated with an excess of triethylorthoformate (TEOF) at high temperatures without the addition of any acid catalysts.[4] In this study, it was reported that the addition of solvents or sulfonic acid catalysts had a deleterious effect in the esterifications of most of the substrates. The esterification of carboxylic acids with N,N-dimethylformamide dialkylacetals has also been well established.[5] The unusually mild esterification of sulfonic acids with a large excess of TEOF has been reported by Just and coworkers.[6] They observed that good yields of the corresponding ester were obtained when the sulfonic acid substrate was allowed to stir at room temperature for 14 hours or heated to reflux for 30 minutes with a very large excess of TEOF (~17 eq.).

We have examined the esterification of both sulfonic and carboxylic acids carefully with TEOA and TEOF. The two reagents show surprising differences in their reactivity with TEOA being a superior reagent for esterification. When TEOA (3 eq.) was added to a solution of p-toluenesulfonic acid ($TsOH{\cdot}H_2O$, 1 eq.) in $CDCl_3$ the formation of ethyl p-toluenesulfonate was complete within minutes as seen by its NMR spectrum. The same reaction with TEOF showed much slower progress and the esterification of TsOH was not complete even after several hours as indicated by our NMR studies. The reactions were repeated on preparative scales (TEOA or TEOF, 3 eq., CH_2Cl_2, 30 min.). The yield of the esterified sulfonic acid that was isolated was much

higher with TEOA (97%) than for TEOF (8%). Complete esterification of sulfonic acids can be achieved by use of large excess of TEOF and much longer reaction times.

The products from TEOA reactions can be isolated in high purities and yields by simple removal of all the excess reagents in vacuo. Direct conversion of the more readily available salts of sulfonic acids to the corresponding esters with TEOA can be accomplished using a one pot procedure. As an example,the sodium salt of heptanesulfonic acid was first treated with excess ethanolic HCl. The ethanol was removed in vacuo and the residue was dissolved in dichloromethane. TEOA (3 eq.) was added to the mixture and stirred for 30 minutes prior to work up. Using this procedure ethyl heptanesulfonate could be prepared in 69% yield. The results of our study are summarized in Table 1. The use of trimethylorthoacetate (TMOA) in these reactions allows the preparation of the corresponding methyl esters.

When a solution of TsOH in ethanolic HCl was stirred at room temperature for 12 hours no ester formation was observed confirming the importance of TEOA in this reaction. It is also interesting to note that N,N-dimethyformamide dimethyacetal was unsuccessful in the esterification of TsOH at room temperature.

Table 1. Esterification of Sulfonic Acids[7,8]

Sulfonic Acid	Reaction Conditions[a]	Product	Yield(%)
p-Toluenesulfonic acid	3 eq TEOA, 30 min	ethyl ester	97
"	3 eq TEOF, 30 min	"	8
"	5 eq TMOA, 30 min	methyl ester	96
Methanesulfonic acid	3 eq TEOA, 30 min	ethyl ester	92
Heptanesulfonic acid, sodium salt	1) EtOH/HCl 2) 3 eq TEOA, 30 min	ethyl ester	69
D-Camphorsulfonic acid	3 eq TEOA, 30 min	ethyl ester	97
"	3 eq TEOF, 30 min	ethyl ester	8
"	5 eq TMOA, 30 min	methyl ester	98

[a]All reactions were carried out at room temperature with CH_2Cl_2 as the solvent

The esterification of carboxylic acids with TEOA in the presence of TsOH [9] as catalyst at room temperature was then examined. When a solution of p-toluic acid was stirred with TEOA (2 eq.) in the presence of TsOH (0.1 eq.) as catalyst in $CDCl_3$, the NMR spectrum showed complete esterification of the catalyst within minutes with no detectable formation of the carboxylate ester. This clearly suggests that sulfonic acids are more rapidly esterified with TEOA than the corresponding carboxylic acid analogs.

However, when carboxylic acids were refluxed in toluene (18-24 hours) in the presense of TEOA (3 eq.) esterification occurred to give high yields of the desired ethyl esters. No acid or base catalysts were required for this reaction. The reaction does proceed in the absence of any solvent by heating the substrate with excess TEOA for several hours. Under comparable reaction conditions, esterifications with TEOF gave poor conversions and led to low yields of the ester products. The addition of catalytic amounts of N,N-dimethylformamide appeared to have no significant effect in the rate of esterification of naphthylacetic acid

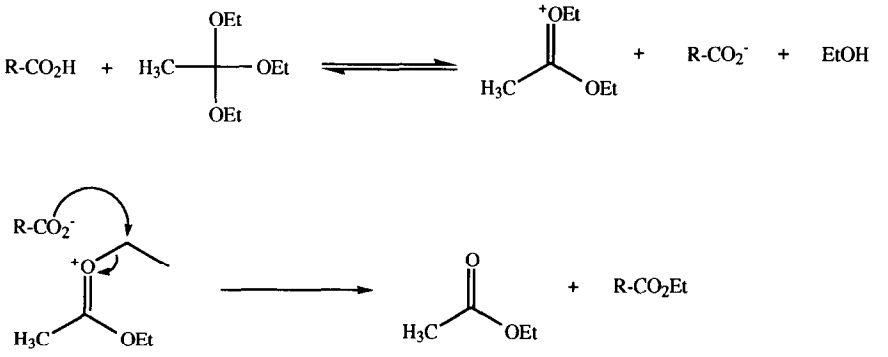
when either TEOA or TEOF was used as the reagent. The esterification of both nicotinic acid and 2,6-dimethylbenzoic acid could be achieved in high yields. The results of our study are shown in Table 2. It is clear from our studies that TEOA rather than TEOF is the preferred reagent for the preparation of esters under neutral conditions.

Table 2. Esterification of Carboxylic Acids [8,10]

Carboxylic Acid	Reaction Conditions[a]	Product	Yield(%)
1-Napthoic acid	3 eq TEOA, 24 h	ethyl ester	89
"	3 eq TEOF, 21 h	"	14
1-Naphthylacetic acid	3 eq TEOA, 24 h	"	92
"	3 eq TEOF, 19 h	"	12
"	3 eq TMOA, 24 h	methyl ester	81
Nicotinic acid	3 eq TEOA, 24 h	ethyl ester	81
"	3 eq TMOA, 24 h	methyl ester	77
2,6 Dimethylbenzoic acid	3 eq TEOA, 24 h	ethyl ester	83
Adipic acid	5 eq TEOA, 24 h	diethyl ester	89
"	5 eq TMOA, 24 h	dimethyl ester	68

[a] All reactions were carried out at 110°C with toluene as the solvent

It is likely that the mechanism of the esterification with TEOA involves O-alkylation as suggested by Just and coworkers [6a] in the case of the esterification of sulfonic acids with TEOF. Also it has been established that esterification of carboxylic acids with dimethyl acetals of dimethylformamide involves O-alkylation of the carboxylate moiety.[5d] Based on these precedents, we feel it is likely that the esterification of carboxylic acids with TEOA proceeds by the mechanism shown in Scheme 1. The fact that no significant rate differences in the esterification of 2,6-dimethylbenzoic acid and benzoic acid was observed is supportive of an O-alkylation mechanism. The enhanced rate of esterification observed for TEOA over TEOF is probably due to the higher stability of its cationic intermediate.



Scheme 1

In conclusion triethylorthoacetate is an ideal reagent for the conversion of sulfonic acids into their ethyl esters rapidly under mild conditions. The esterification of carboxylic acids by this reagent is also conveniently carried out in high yields without the addition of any base or acid catalysts. Use of trimethylorthoacetate instead of TEOA in this reaction allows the ready preparation of the corresponding methyl esters. Investigations are in progress to more clearly identify the uses and limitations of these reagents.

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7. Representative procedure for sulfonic acid esterification. Ethyl p-toluenesulfonate: To a solution of p-toluenesulfonic acid (5.06 g, 27 mmol) in dichloromethane (50 mL) was added triethylorthoacetate (14.8 mL, 71 mmol, 3 eq) dropwise. The reaction mixture was stirred at room temperature for thirty minutes. The solvent and excess reagent were removed in vacuo to give a yellow oil. Kugelrohr distillation of the product at 110°C (0.7 torr) gave the ethyl ester (5.19 g, 97%) as a colorless liquid.
8. Spectroscopic data of all products were in agreement with their assigned structures.
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10. Representative procedure for carboxylic acid esterification. Ethyl 1-naphthoate: To a solution of 1-naphthoic acid (5.0 g, 29 mmol) in toluene (35 mL) was added triethylorthoacetate (16.0 mL, 87 mmol, 3 eq) dropwise. The reaction mixture was refluxed for 24 hours. After cooling, 2M HCl (30 mL) was added to the mixture. The organic extract was washed with saturated $NaHCO_3$ (1x30 mL) and brine (1x30 mL) and dried with $MgSO_4$. The solvent and excess reagent were removed in vacuo to give a brown oil. Kugelrohr distillation of the product at 100°C (0.45 torr) gave the ethyl ester (5.15 g, 89%) as a colorless liquid.

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