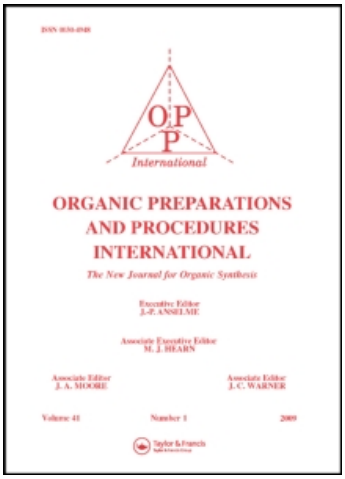


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# A NEW RAPID ESTERIFICATION PROCEDURE UTILIZING EXCEPTIONALLY MILD REACTION CONDITIONS

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# A NEW RAPID ESTERIFICATION PROCEDURE UTILIZING EXCEPTIONALLY MILD REACTION CONDITIONS

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The esterification of carboxylic acids is a synthetic transformation of major importance. Several methods are available for the esterification of carboxylic acids with alkyl halides. However, the simple procedure utilizing the reaction of metal salts of carboxylic acids with alkyl halides is of limited synthetic utility.[1] The recent publication[2] by Ono and his coworkers of the rapid esterification of carboxylic acids with alkyl halides in benzene at 25° induced by 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU)[3] persuades us to publish our own studies in this area. The

$$RCO_2H + R'X + DBU \longrightarrow RCO_2R' + DBUH^+X^-$$

procedure we developed utilizes acetonitrile as the reaction medium. The reactions in this solvent are much faster than those in benzene.

Indeed, we observed that mixtures of representative carboxylic acids and DBU react rapidly (1-2 hrs) at 25° with representative alkyl halides to give essentially quantitative yields of esters. On the other hand, under similar conditions, the presence of equimolar amounts of

tertiary amines, such as pyridine and triethylamine, fail to induce esterification. The reaction presumably involves the formation of $RCO_2^-DBUH^+$ with the high reactivity of the carboxylate anion reflecting an exceptional absence of association of the anion with the delocalized cation.

Reaction of benzoic acid with methyl iodide in the presence of DBU was carried out in three different solvents: diethyl ether, benzene and acetonitrile. The yields of methyl benzoate realized after 1 hr of reaction was 60%, 82% and 90%, respectively. Acetonitrile was selected as the solvent of choice. The reaction is faster in this solvent and the solvent is free of the toxic and flammability hazards of the other two media explored.

The reaction appears to be broadly applicable, apparently handling with ease representative primary and secondary halides. Similarly, it handles hindered acids, such as pivalic and mesitoic. No tautomerization was observed in the esterification of the relatively labile acid, 3-butenoic acid. Finally, the carboxylic group in *p*-dimethylaminobenzoic acid is esterified without detectable attack on the amino group. The use from theoretical to 25% excess DBU and from theoretical to 20% excess alkyl halide had no significant effects upon the yields.

This procedure, using acetonitrile as solvent, should be preferred to procedures utilizing highly toxic solvents such as benzene or HMPA and appears to be the procedure of choice for such esterification.

## EXPERIMENTAL

$^1H$ NMR spectra were recorded on a Varian T-60 spectrometer with tetramethylsilane as an internal standard. Solvents and DBU were purified by distillation.

Preparation of Methyl Benzoate. Typical Procedure.- In a dried 50-mL round-bottom flask fitted with a magnetic stirring bar and a septum inlet tube, connected to a mercury bubbler, was placed 2.44 g (20 mmol) of benz-

oic acid and 20 mL of acetonitrile. To the well stirred solution was added with the help of a syringe 3.04 g (20 mmol) of DBU (Aldrich). Then 3.13 g (22 mmol) of methyl iodide was added and the reaction mixture was stirred for 1 hr at room temperature (∿ 25°). The reaction mixture was diluted with 20 mL of water and extracted twice with 20-mL portions of ethyl ether.

Table.- Esterification of Carboxylic Acids with Alkyl Halides

| Carboxylic Acid | Alkyl halide | Time (hrs) | Ester | Yield (%) |
|---|---|---|---|---|
| Hexanoic | EtBr | 2 | Ethyl hexanoate | 96 |
| Cyclopropane- | MeI | 1 | Methylcyclopropane-carboxylate | 85 |
| Cyclohexane- | EtBr | 2 | Ethyl cyclohexane-carboxylate | 96 |
| Benzoic | MeI | 1 | Methyl benzoate | 90 |
| | EtBr | 2 | Ethyl benzoate | 97 |
| | EtI | 1 | Ethyl benzoate | 97 |
| | *i*-$C_3H_7I$ | 1 | Isopropyl benzoate | 90 |
| | *s*-$C_4H_9Br$ | 4 | *sec*-Butyl benzoate | 87 |
| *p*-Anisoic | EtBr | 2 | Ethyl *p*-anisoate | 95 |
| Mesitoic | MeI | 1 | Methyl mesitoate | 96 |
| Pivalic | MeI | 1 | Methyl pivaloate | 87 |
| 3-Butenoic | MeI | 1 | Methyl 3-butenoate | 86 |
| *p*-Dimethylaminobenzoic | EtBr | 2 | Ethyl *p*-dimethylamino-benzoate | 88 |

The combined ethereal extracts were washed twice with 20-mL portions of water. After having been dried over anhydrous magnesium sulfate, the solution was evaporated to provide 2.65 g (97%) of essentially pure methyl benzoate, as indicated by $^1H$ NMR. Distillation provided 2.45 g (90%) of pure methyl benzoate, bp 198-198.5°, lit.[4] bp 198-199.

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