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A SIMPLE QUANTITATIVE METHOD FOR THE ESTERIFICATION OF CARBOXYLIC ACIDS

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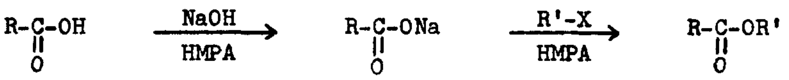
A recent report[1] on the esterification of carboxylic acids by reaction of their salts with alkyl halides prompts us to report our observations which we realized while investigating the reduction-alkylation of α,β-unsaturated acids in hexamethylphosphoramide.[2] We wish to report that carboxylic acids can be quantitatively converted to esters by reaction of their sodium salts with alkyl bromides or iodides in hexamethylphosphoramide (HMPA) at room temperature. Results obtained with various acids are shown in the Table.

The speed and simplicity of this method for the preparation of methyl esters can be demonstrated by the following reaction which was carried out in a separatory funnel. To a solution of 10 mmoles of mesitoic acid in 25 mls of HMPA was added 20 mmoles of sodium hydroxide (added as a 25% aqueous solution). After shaking the solution for 5 minutes, 40 mmoles of methyl iodide were added, and the solution was shaken another 5 minutes. Then 50 mls of 5% HCl in water was added, and the solution was subjected to an ether work-up similar to that described in the general procedure given below. The crude product was analyzed by IR and glpc which revealed that only methyl mesitoate was present and that the absolute yield of the ester was 99%.

The time required for complete esterification varied depending on the carboxylic acid and alkyl halide used. Reaction of the sodium salt of octanoic acid with methyl iodide (4 mole equivalents) required 15 minutes for complete esterification. This is longer than in the case of mesitoic acid probably

TABLE



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}OH} \xrightarrow[\mathrm{HMPA}]{\mathrm{NaOH}} \mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}ONa} \xrightarrow[\mathrm{HMPA}]{\mathrm{R'{-}X}} \mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}OR'}$$

Carboxylic Acid	Alkylating Agent	% Yield (absolute) of Corresponding Ester[a]
mesitoic acid	methyl iodide	99,98
" "	isopropyl iodide	100
" "	isopropyl bromide	98
α-methylhydrocinnamic acid	methyl iodide	98
2-ethylbutanoic acid	ethyl iodide	96[b]
" "	isopropyl iodide	99[b]
o-benzoylbenzoic acid	ethyl bromide	99[c]
trimethylacetic acid	sec-butyl bromide	97[d]
triphenylacetic acid	ethyl bromide	98[c]
octanoic acid	methyl iodide	96
3-methyl-2-butenoic acid	methyl iodide	95
butanoic acid	tert-butyl bromide	trace
cyclohexanecarboxylic acid	cyclohexyl iodide	0

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[a] Absolute yield of liquid esters determined by glpc.

[b] Sodium hydride used to prepare salt of acid (1.1 to 2.0 mole equivalents).

[c] Yields based on crude crystalline product since melting points in excellent agreement with literature values.

[d] Reaction time was 30 hours. Twenty hours was insufficient.

because sodium octanoate was not completely soluble in HMPA. The sodium salts of the other acids in the Table were all soluble in HMPA except for butanoic acid and cyclohexanecarboxylic acid. Reaction of sodium mesitoate with isopropyl bromide was only about 30% complete after stirring for three hours at room temperature. The reaction was complete after 24 hours. Isopropyl iodide caused quantitative esterification of sodium mesitoate in less than one hour at room temperature. The reaction times we observed for sodium salts in HMPA at room temperature are much faster than those reported for potassium or sodium salts in 50% ethanol-HMPA at 50°.[1]

As expected tertiary halides failed to give esters in good yield. Reaction of sodium butanoate with tert-butyl bromide gave 2-methylpropene and only a trace of ester. A reaction between the sodium salt of cyclohexanecarboxylic acid and cyclohexyl iodide also failed.

The general procedure for the esterifications was as follows. To a solution of 20 mmoles of the carboxylic acid in 50 mls of HMPA was added 30 mmoles of sodium hydroxide (added as a 25% aqueous solution) or sodium hydride (50% dispersion in mineral oil), and the solution was stirred at room temperature for one hour. Then 80 mmoles of the alkyl halide were added, and the solution was allowed to stir overnight (20-24 hours) at room temperature. This reaction time is probably necessary for the esterifications in the Table using alkyl bromides. When alkyl iodides are used, the esterifications appear to be complete in less than one hour. The solution was then poured into 100 mls of 5% HCl solution and extracted with two 75 ml portions of ether. The combined ether extracts were washed twice with 25 ml portions of water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure. In some reactions the amount of base used to prepare the salts of the acids varied from 1.1 to 2.0 mole equivalents, but this had no effect on the yields. It was found that the crude ester products from o-benzoylbenzoic acid and triphenylacetic acid were crystalline and even without recrystallization gave sharp melting points in perfect agreement with literature values.[3]

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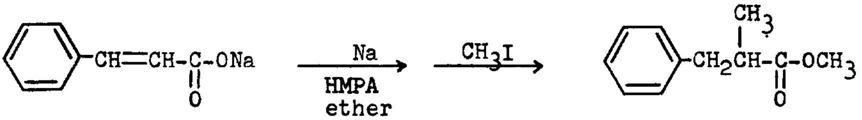
FOOTNOTES AND REFERENCES

1. P. E. **Pfeffer**, T. A. Foglia, P. A. Barr, I. Schmeltz, and L. S. Silbert, Tetrahedron Letters, 4063 (1972).
2. We have found that the sodium salts of certain α,β-unsaturated acids can be reduced to carboxylic acid dianions with sodium in HMPA-ether (2:1). Addition of alkyl halides results in α-alkylation and esterification.



35% yield

3. "Dictionary of Organic Compounds," 4th ed., Oxford University Press, New York, N. Y., 1965.