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ESTERIFICATION WITH MIXED ANHYDRIDE ACTIVATED BY INTRAMOLECULAR CYCLIZATION

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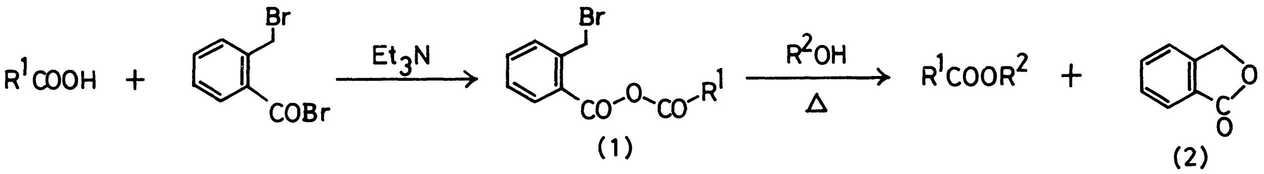
Mixed anhydrides, prepared from α-bromo-o-toluoyl bromide and carboxylic acids, were activated by an intramolecular cyclization when heated in the presence of alcohols, giving the corresponding carboxylic esters in good yield with the elimination of phthalide.

The acylation of alcohols by means of acid anhydrides usually needs the base or the acid catalysts. Recently we reported the rapid synthesis of carboxylic esters[1)] and thiol esters[2)] using the carboxylic 2,4,6-trichlorobenzoic anhydrides, but in these cases also, the presence of fairly basic 4-dimethylaminopyridine was essential. In the present communication, we wish to describe a different type of mixed anhydrides (1) which do not need such catalysts but are activated by mere heating.

When solutions of the mixed anhydrides prepared in situ from α-bromo-o-toluoyl bromide and carboxylic acids were heated at 80° to 145°C in benzene or tetramethylurea in the presence of alcohols, the corresponding carboxylic esters were formed in good yields. The results are summarized in the Table. The elimination of phthalide (2) by an intramolecular cyclization is considered to be the driving force of this reaction. The formation of phthalide and alkyl bromides from alkyl α-bromo-o-toluate by heating has been already reported.[3,4)] By the present method, sterically crowded t-butyl pivalate could be prepared which was only difficultly formed by other anhydride methods.[5)] When prolonged reaction time is required, it is advantageous to add 2,6-lutidine to quench the hydrobromic acid formed in the reaction, which slowly decomposes the ester once formed. Pyridine or triethylamine retarded the reaction (example: entry 5 in the Table).



The typical procedure of the esterification is as follows (entry 6).

Ethyl 2-methylpentanoate: α-Bromo-o-toluoyl bromide[3)] (150 μl, 1 mmol) was added to a stirred mixture of 2-methylpentanoic acid (126 μl, 1 mmol), triethylamine (140 μl, 1 mmol), and benzene (1 ml). After one hour, the reaction mixture was filtered through a dry celite column. Ethanol (58 μl, 1 mmol) was added to the

Table. Reaction Conditions and Yields of Esters

	Acid[a] R^1 in R^1COOH	Alcohol[a] R^2 in R^2OH	Solvent	Temp. (°C)	Time (min)	Addendum	Yields of Esters(%)[b]
1	CH_3CH_2	CH_3CH_2	TMU[c]	100	26		99
2	$CH_3CH_2CH_2$	$CH_3CH_2(CH_3)CH$	Benzene	80	80		100(81)
3	$(CH_3)_2CH$	$(CH_3)_3C$	Benzene	80	40		80
4	$(CH_3)_2CH$	$(CH_3)_3C$	TMU[c]	80	55		91
5	$(CH_3)_2CH$	$(CH_3)_3C$	TMU[c]	80	200	Pyridine	59
6	$CH_3CH_2CH_2(CH_3)CH$	CH_3CH_2	Benzene	80	80		99(88)
7	$(CH_3)_3C$	$(CH_3)_3C$	TMU[c]	100	380	LUT[d]	87
8	C_6H_5	$C_6H_5CH_2$	TMU[c]	145	210	LUT[d]	(70)
9	$(CH_3)_2CH$	C_6H_5	Benzene	80	120	LUT[d]	86(91)

a) Reactions were carried out in a 0.5 mmol scale for the GLPC determinations and in an 1 mmol scale for the isolation experiments.
b) Yields were determined by GLPC by comparing with the internal standards. Isolated yields were given in parentheses. All products were characterized by comparison with the authentic samples.
c) TMU stands for N,N,N',N'-tetramethylurea.
d) One equivalent of 2,6-lutidine was added as the quencher of hydrobromic acid.

filtrate and the mixture was stirred at 80°C for 80 min. The reaction mixture was diluted with pentane and filtered to remove a larg portion of phthalide (93 mg, 70%; mp of once recrystallized material, 73°C). The filtrate was concentrated and distilled at 90°C/15 mmHg (bath temperature) to give ethyl 2-methylpentanoate (127 mg, 88%).

For the isolation of benzyl benzoate (entry 8), the reaction mixture was diluted with benzene and filtered, and the solvent was removed under diminished pressure. The ester was isolated by preparative TLC (silica gel) of the residue.

Further studies on the application of this type of anhydrides are in progress.

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References and Notes

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5) For example, it has been reported that t-butyl pivalate could not be prepared by the anhydride method under the presence of 4-dimethylaminopyridine (G. Hofle and W. Steglich, Synthesis, 1972, 619.).

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