Esterification of Heterocyclic Carboxylic Acids Using a Boron Trifluoride Etherate-Alcohol Reagent

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Although the boron trifluoride-methanol complex is used commonly for the conversion of simple carboxylic acids to their methyl esters prior to G.L.C. analysis[1], recently it has been reported to be a useful reagent for preparative-scale esterifications. A mixture of an alcohol and boron trifluoride etherate has been found to be an effective reagent in the direct esterification of 4-aminobenzoic acid[2], unsaturated organic acids[3], biphenyl-4,4′-dicarboxylic acid[4], and 1,4-dihydrobenzoic acid. Trialkyloxonium tetrafluoroborate has also been recommended as an esterification reagent for carboxylic acids including sterically hindered acids[5]; the reaction, however, is limited to the preparation of the methyl and ethyl esters.

We have now found that the boron trifluoride etherate-alcohol procedure is quite unique for the esterification of heterocyclic carboxylic acids.

$$R^1{-}COOH \xrightarrow{BF_3 \cdot (C_2H_5)_2O/R^2{-}OH} R^1{-}COOR^2$$

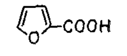
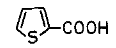
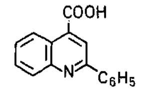
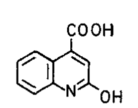
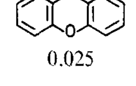
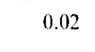
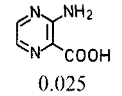
R^1 = heterocyclic group
R^2 = alkyl

The many unexpected difficulties associated with the usual procedures for the esterification of carboxylic acids[5] are encountered in the esterification of heterocyclic acids also; in addition, several heterocyclic ring systems are susceptible to hydrolytic degradation in the presence of strong acids and bases[6] and present further difficulties. Unlike the conventional Fischer esterification procedure where other functionality in the molecule[7] or the heterocyclic ring system itself may be sensitive to the strongly acidic conditions of the reaction[6] and leads to invariably low yields of esters[8,9,10], the boron trifluoride reaction is thorough and mild and the acids are converted cleanly to their esters. Other functional groups present in addition to the carboxyl moiety are not affected. The boron trifluoride etherate-alcohol procedure thus offers great potential as a general method for the facile esterification of heterocyclic carboxylic acids in a direct, single step reaction, using the alcohols themselves.

The results of esterification of a number of acids having different heterocyclic ring systems are presented in the Table.

Table. Esterification of Heterocyclic Carboxylic Acids Using a Boron Trifluoride Etherate-Alcohol Reagent

$$R^1\text{—COOH} \xrightarrow{BF_3 \cdot (C_2H_5)_2O/R^2\text{—OH}} R^1\text{—COOR}^2$$

R^1—COOH mol	R^2	$BF_3 \cdot (C_2H_5)_2O$[a] mol	Time of reflux hr	Yield of ester[b] %	m. p. or b. p.[c]
 0.05	CH_3[d]	0.1	4	81	b. p. 78°/6.5 mm (b. p. 181.3°)
	C_2H_5	0.1	4	76	m. p. 35–36° (34°)
	n-C_3H_7	0.1	4	74	b. p. 78–79°/2.6 mm (b. p. 210.9°)
 0.05	CH_3	0.1	4	77	b. p. 80–82°/2.5 mm (40°/0.5 mm)
	C_2H_5	0.1	4	64	b. p. 97°/2.75 mm (b. p. 218°)
			24	83	
 0.025	CH_3	0.05	21	38	m. p. 50–52° (61°)[e]
			68	72	
	n-C_3H_7				
	(0.3 mol)	0.05	74	78	m. p. 62–63° (63–64°)
	(0.5 mol)	0.05	48	77	
	n-C_4H_9	0.05	48	71	m. p. 56–57° (56–57°)
	c-C_6H_{11}[f]	0.05	48	67	m. p. 66–67°
 0.025	CH_3	0.075	24	96	m. p. 248–251° (242–243°)
	C_2H_5	0.075	24	81	m. p. 207–210° (206–207°)
	n-C_3H_7[f]	0.075	18	91	m. p. 168–169°
			10	72	
	n-C_4H_9[f]	0.075	4	90	m. p. 151–154°
	i-C_3H_7[f]	0.075	24	25	m. p. 186–190°
 0.025	CH_3	0.05	24	87	m. p. 84–85° (85–86°)
	C_2H_5[f]	0.05	1.5	95	m. p. 55–57°
	$-CH_2-CH_2-OCH_3$[f]	0.05	1.5	78	b. p. 184–186°/0.9 mm
	n-C_3H_7[f]	0.05	20	70[g]	b. p. 202–204°/1.5 mm
 0.02	CH_3	0.06	3.5	81	m. p. 116–118° (116–117°)
	C_2H_5	0.06	1.25	77	m. p. 93–94.5° (94°)
	n-C_3H_7[f]	0.06	1.75	87	m. p. 71–72°
	n-C_4H_9[f]	0.06	1.5	92	m. p. 48–49°
	i-C_3H_7[f]	0.06	5	79	m. p. 84–86°
 0.025	CH_3[f]	0.1	24	45[h]	m. p. 170–171°

[a] The amount is determined by the number and nature of the functional groups present, an additional equivalent of $BF_3 \cdot (C_2H_5)_2O$ being required for complex formation with each functional group including the heteroatom of the ring system that has a pair of free electrons available for coordination with the $BF_3 \cdot (C_2H_5)_2O$.

[b] Refer to the distilled or crystallized products.

[c] The literature m.p. or b.p. is given in parentheses.

[d] See Ref.[11]. This appears to be the only report on the esterification of a heterocyclic acid using a boron trifluoride reagent; the methyl esters of furoic and nicotinic acids have been obtained using a boron trifluoride-methanol complex.

[e] The lit. m.p. for this ester does not appear to be correct; our ester has an m.p. 50–52° even after repeated crystallization and is identical with a sample prepared by the action of methanol on the acid chloride.

[f] These esters do not appear to have been described in the literature and satisfactory elemental (C, H, and N) and I.R. analyses have been obtained for these compounds.

[g] The ester undergoes decomposition during distillation and a drop in the yield results; yield of crude product is 90%.

[h] The water-soluble ester was isolated by concentrating the reaction mixture under reduced pressure, adding water (20 ml), and then saturating the mixture with solid sodium carbonate. Repeated extraction with ether yielded the ester.

Esterification of Heterocyclic Carboxylic Acids; General Procedure:

The reaction mixture comprising the acid, boron trifluoride etherate, and the appropriate alcohol (10 times in excess of the boron trifluoride etherate) was refluxed for a period of time, which was determined by the reactivity of the acid. The esters were precipitated by dilution with water, occasionally after removal of the excess alcohol under reduced pressure, and followed by filtration or extraction with ether. Unreacted acid was removed by trituration of the crude ester or extraction of the ethereal solution with a dilute solution of sodium carbonate and final purification effected by crystallization from appropriate solvents or by distillation under reduced pressure.

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