Table I—Effect of Extracts of Various Species of Coelenterates on Rat Atria

Species	Source	Concentration, ppm	Percent Increase, Inotropic[a]	Percent Increase, Chronotropic[a]
Boloceroides mcmurrichi (Kwietniewski)	Oahu, Hawaii	—[b]	20–51	0
Palythoa psammophilia Walsh and Bowers	Oahu, Hawaii	—[b]	0	0
Zoanthus pacificus Walsh and Bowers	Oahu, Hawaii	—[b]	0	0
Macranthea cookei Verrill	Oahu, Hawaii	—[b]	0	0
Tealia coriacea (Cuvier)	Bodega Bay, Calif.	500	>100	0
Tealia lofotensis (Danielssen)	Bodega Bay, Calif.	350	10–20	0
Metridium senile (L.)	Bodega Bay, Calif.	50	125–150	67
Anthopleura xanthogrammica (Brandt)	Bodega Bay, Calif.	119	300[c]	30
Anthopleura elegantissima (Brandt)	Bodega Bay, Calif.	88	230[d]	14
Tealiopsis nigrescens Verrill	Oahu, Hawaii	100	230	85
Stoichactis kenti Haddon and Shackleton[e]	Tahiti	10	50–85	0–30
Tubastrea aurea Quoy and Gaimard	Oahu, Hawaii	100	210	43
Cassiopeia mertensi Brandt	Oahu, Hawaii	100	0	0

[a] Increases were noted for at least 5 min. [b] A 0.1-ml crude extract diluted 200:1. [c] Increase observed for 70 min, dropping to 170% at 70 min. See Fig. 1. [d] Increase observed for 30 min, dropping to 100% at 30 min. See Fig. 1. [e] Purified fraction. Procedure described in Turlapaty *et al.* (6).

not related to any adrenergic mechanism and that the compound(s) probably acts directly on the heart muscle.

The isolation, characterization, mode of action, dose–response, and other pharmacological studies of the active principle(s) are being pursued.

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New Compounds: Convenient Selective Esterification of Aromatic Carboxylic Acids Bearing Other Reactive Groups Using a Boron Trifluoride Etherate–Alcohol Reagent

PANKAJA K. KADABA

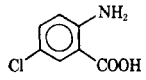
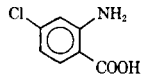
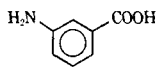
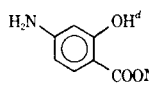
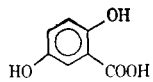
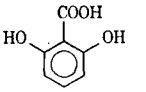
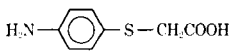
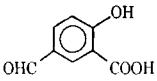
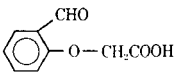
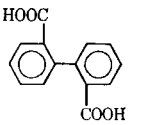
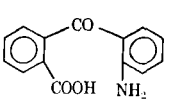
Abstract □ A mixture of commercial boron trifluoride etherate and an alcohol functions as an effective reagent in the direct esterification of a number of aromatic carboxylic acids bearing additional functional groups such as —OH, —NH_2, >C=O, —O—, and —S—, either alone or in conjunction with another group. Unlike the conventional Fischer esterification procedure where strongly acidic conditions prevail, the boron trifluoride etherate–alcohol reagent is unique in that it is both mild and effective. It esterifies the carboxyl group without affecting the other functionality in the molecule or the stability of the acid itself. The boron trifluoride procedure does not suffer from a lack of generality; it satisfactorily meets the esterification requirements of a greater number of different classes of carboxylic acids than does any other single reagent known. The method offers a simple and convenient esterification route for organic acids in general, in a direct, single-step reaction, using the alcohols themselves.

Keyphrases □ Carboxylic acids (aromatic) with reactive groups—selective esterification using boron trifluoride etherate–alcohol □ Esterification—aromatic carboxylic acids bearing other reactive groups, boron trifluoride etherate–alcohol reagent □ Boron trifluoride etherate–alcohol—used as reagent for convenient selective esterification of aromatic carboxylic acids with reactive groups

Although boron trifluoride complexed with methanol, $BF_3 \cdot CH_3OH$, is a common esterification reagent for stable carboxylic acids prior to GLC analysis (1), it is not generally considered useful for preparative scale esterifications. Recently, however, a mixture of an alcohol and commercial boron trifluoride etherate

Table I—Esterification of Carboxylic Acids Bearing Other Functional Groups Using a Boron Trifluoride Etherate–Alcohol Reagent

$$R_1COOH + R_2OH \xrightarrow{BF_3\cdot(C_2H_5)_2O} R_1COOR_2 + H_2O$$

R_1COOH	Mole	R_2	$BF_3\cdot(C_2H_5)_2O$, mole	Time of Reflux, hr	Yield of Ester[a], %	Melting Point[b]
	0.05	CH_3	0.1	30	29	68–69°[c] (76°)
	0.025	CH_3	0.05	30	30	66–68° (68–69°)
	0.025	CH_3	0.075	24	22	66–68°
	0.0125	CH_3	0.025	96	58	64–66°
	0.05	CH_3	0.1	24	26	37–38° (39°)
	0.1	CH_3	0.4	17	84[e]	120–122° (120–121°)
	0.1	CH_3	0.3	19	84	120–122°
	0.1	CH_3	0.1	19	15	118–122°
	0.05	C_2H_5	0.15	48	52	114–115° (114–115°)
	0.05	n-C_3H_7[f1]	0.15	24	41	104–105°
Hydrochloride salt of acid	0.05	CH_3	0.1	24	48	118–122°
	0.05	CH_3	0.15	24	81	85–87° (88°)
	0.05	C_2H_5	0.15	18	79	77–78° (77°)
	0.05	n-C_3H_7[f2]	0.15	21	80	62–64°
	0.05	$CH_2CH_2OCH_3$[f3]	0.15	24	76	88–90°
	0.05	n-C_4H_9[f4]	0.15	24	69	65–66.5°
	0.05	CH_3	0.15	52	55[g]	70–72° (69–71°)
	0.05	C_2H_5[f5]	0.15	66	34	51°
	0.05	n-C_3H_7[f6]	0.15	51	32	37–39°
	0.05	CH_3[f7]	0.1	23	73[h]	192–195°[j]
	0.1	CH_3	0.2	24	78[i]	192–195°[j]
	0.05	C_2H_5	0.1	23	60[i]	152–154°[j,k]
	0.02	CH_3	0.06	24	78[l]	81–82° (82–83°)
	0.02	C_2H_5	0.06	23	68[l]	69–69.5°[m] (75°)
	0.02	CH_3	0.04	20	72	55° (55°)
	0.02	CH_3	0.04	24	78	72–74° (74°)
	0.02	CH_3	0.06	18	—[n]	—

[a] Refers to crystallized products. [b] The literature melting points are given in parentheses. [c] The product gave the same melting point after repeated crystallizations. [d] Reference 8 reports the preparation of the methyl, ethyl, and isopropyl esters of this acid using 4.5 moles of $BF_3\cdot(C_2H_5)_2O$ for each mole of acid. By allowing the reaction mixture to stand at room temperature for 10–30 days, approximately 70% yields of esters have been obtained. [e] Reference 8. The preparation of the methyl ester with sulfuric acid in methyl alcohol gave less than 10% yield. The primary product was *m*-aminophenol. [f1–f7] The melting points for these esters could not be located in the literature. Characterization was made by elemental and IR analysis. *f*1 calc.: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.51; H, 6.73; N, 7.08. *f*2 calc.: C, 61.21; H, 6.17. Found: C, 61.21; H, 6.18. *f*3 calc.: C, 56.60; H, 5.70. Found: C, 56.68; H, 5.65. *f*4 calc.: C, 62.84; H, 6.71. Found: C, 62.78; H, 6.69. *f*5 calc.: C, 59.33; H, 5.53. Found: C, 59.25; H, 5.50. *f*6 calc.: C, 61.21; H, 6.17. Found: C, 61.35; H, 6.20. *f*7 calc.: C, 46.26; H, 5.19. Found: C, 46.21; H, 5.14. [g] Reference 9 reports the same yield after 4 days of reflux using a boron trifluoride–methanol reagent (Matheson, Coleman and Bell). Fischer esterification of the acid gave only 36% yield. [h] The ester was isolated as the hydrochloride salt. The reaction mixture was treated with water (50 ml) and made basic to litmus by adding solid sodium carbonate. The ester, partially soluble in water, was recovered by repeated extraction with ether and converted to the hydrochloride salt by addition of concentrated hydrochloric acid to the dried ethereal solution. [i] In these runs, the reaction mixture was well cooled and treated directly with ether followed by concentrated hydrochloric acid, when the hydrochloride salt of the ester separated out as beautiful crystals. [j] Melting point of the hydrochloride salt. [k] *Anal.*—Calc.: C, 48.48; H, 5.66; S, 12.93. Found: C, 48.31; H, 5.57; S, 12.98. [l] The ester was not treated with sodium carbonate. The crude product obtained by dilution of the reaction mixture was recrystallized from ethanol to give the pure ester. The product gave the phenylhydrazone in quantitative yield, mp 120–121°. [m] A sample purified through the bisulfite addition product had the same melting point. [n] The acid yielded the lactam in 78% yield, mp 252–254° [lit. (11) mp 254–255°]. The boron trifluoride etherate appears to aid lactam formation, since the same reaction performed under identical conditions in the absence of $BF_3\cdot(C_2H_5)_2O$ gives only 26% of the lactam, the rest being unchanged acid.

was found to be an effective reagent in the direct esterification of 4-aminobenzoic acid (2), unsaturated organic acids (3, 4), and heterocyclic carboxylic acids (5). Unlike the conventional proton-catalyzed esterifications, where strongly acidic conditions prevail, the boron trifluoride–alcohol procedure is thorough and mild; the reaction is selective at the carboxyl group and the acids are converted cleanly to their esters.

DISCUSSION

Esterification is an important reaction frequently used in biochemical and pharmaceutical research and in medicinal chemistry. However, the usual procedures for the esterification of carboxylic acids are often attendant with unexpected difficulties (6). For instance, in the case of substituted acids, the other functionality in the molecule may be sensitive to the strongly acidic conditions of the standard methods (7) or the acid itself may undergo decomposition (8). Two-step esterification procedures involving reaction of the silver salts of the acids with alkyl halides may help to overcome some difficulties but are expensive (9).

The alkyl esters of a number of aromatic acids, bearing additional functional groups such as —OH, —NH_2, >C=O (as CHO), —O—, and —S— which are susceptible to attack in conventional procedures, are useful as intermediates in the synthesis of biologically interesting heterocycles[1] (10). These acids can be conveniently esterified, using the mild and inexpensive boron trifluoride etherate–alcohol reagent, in a single-step reaction. The results (Table I) indicate that the reagent is effective in the direct esterification of the carboxyl group without affecting other functional groups or the stability of the acids themselves. The present investigation, along with those conducted earlier (2, 3, 5) clearly indicates that the boron trifluoride etherate–alcohol reagent is unique in that it is both mild and effective and it does not suffer from a lack of generality as do other methods (6). It satisfactorily meets the esterification requirements of more classes of carboxylic acids than does any other single reagent known. The boron trifluoride etherate–alcohol procedure offers a simple and convenient esterification route for organic acids in general, in a direct, single-step reaction, using the alcohols themselves.

EXPERIMENTAL

A mixture of the acid, the appropriate alcohol, and boron trifluoride etherate was refluxed for a period of time determined by the reactivity of the acid.

The amount of boron trifluoride etherate to be used was determined by the number and nature of the functional groups present. Groups such as —OH, —NH_2, and >C=O each required an additional equivalent of boron trifluoride etherate for complex formation. Thus, for 1 mole of sodium *p*-aminosalicylate, 3 moles of boron trifluoride etherate should be employed for good results; reducing the reagent to 1 mole reduced the yield of ester from 84% to a mere 15% of low quality material (Table I). When the acid was used in the form of the hydrochloride salt, 2 moles of boron trifluoride etherate was sufficient in theory; however, due to the insoluble nature of the hydrochloride, a heterogeneous reaction mixture resulted followed by lower yields.

In the case of the anthranilic acids and the phenoxy- and phenylmercaptoacetic acids, 2 moles of boron trifluoride etherate seemed sufficient (Table I).

In all cases, the alcohols were used 10 times in excess of the boron trifluoride etherate.

The esters were precipitated by diluting the cooled reaction mixture with water or a 10% solution of sodium carbonate, occasionally after removal of the excess alcohol under reduced pressure, followed by filtration or extraction with ether (whichever was more convenient). To remove unreacted acid, esters obtained by dilution with water were triturated with a dilute solution of sodium carbonate. However, sodium carbonate should be used very sparingly in the case of the hydroxy acids, especially formylsalicylic acid where the hydroxyl group was so acidic that the esters showed a tendency to dissolve in sodium carbonate. Final purification of the esters was effected by crystallization from appropriate solvents.

In the case of *p*-aminophenylmercaptoacetic acid, it was found more convenient to isolate the esters as their hydrochloride salts.

o-Anthraniloylbenzoic acid yielded the lactam (11); there was no ester formation.

[1] Unpublished data.

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