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LETTERS

Esterification of carboxylic acids with boron trichloride

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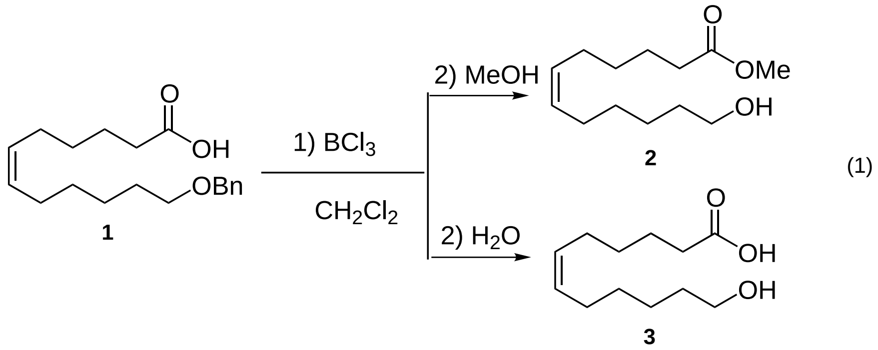
Abstract—Treatment of carboxylic acids with boron trichloride followed by addition of alcohol provides the carboxylic ester. This esterification, following BCl_3 ether or ester O–C cleavage reaction conditions, proceeds cleanly in good yields with most substrates. Cleavage of benzyl esters with boron trichloride then treating with methanol affords the methyl ester. © 2001 Published by Elsevier Science Ltd.

Esterification of carboxylic acids using protic and Lewis acids is a common, fundamental process in organic synthesis.[1–3] Likewise, Lewis acids are employed to cleave some esters as well as ethers.[2,4–7] Under the reaction conditions for *O*-debenzylation, we find that carboxylic acids also undergo esterification. Treatment of the benzyl ether **1** with boron trichloride and then quenching with methanol[5] does not produce the olefinic-acid **3**, but yields the enol-ester **2**. Quenching with water, however, does produce the *seco*-acid **3** (Scheme 1). We report herein an efficient, versatile method for the esterification of carboxylic acids.

It is our observation that carboxylic acids, in general, form the methyl ester (Table 1) in good yield when 1–4 equiv. of boron trichloride are employed. Trichloroborane (1 equiv.) with simple acids, phenylacetic acid (**4a**) for example, forms the ester in good yield. The esterification of cinnamic and aryl acids requires a large excess of boron trichloride. Consequently, when the amount of boron trichloride is reduced, the yields are also reduced. It appears that competition for trichloroborane by multiple Lewis base sites is overcome by addition of an excess of BCl_3, which results in increased yields of the respective ether. In the case of phenolic acids **4b** and **4c**, which have two Lewis base sites, increasing the number of equivalents does not result in increased yields of ester. In all other cases, acids **4d**–**g** with multiple Lewis base sites, including the pyridyl acid **4g**, excess reagent affords good yields of ester **5d**–**g**. It is noteworthy that with 1–3 equiv. of BCl_3, *m*-methoxy acid **4e** forms ester **5e** in low yield and there is also considerable methyl ether cleavage. The ratio of the resultant ether **5e** to methyl 3-hydroxybenzoate (**6**) is approximately 1.5:1.

Cleavage of hindered methyl ethers is efficient with boron trichloride,[8,9] and although not hindered, the



Scheme 1.

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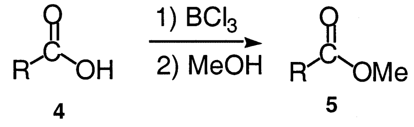
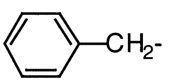
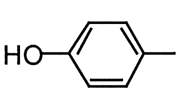
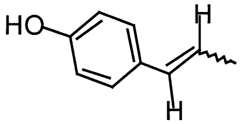
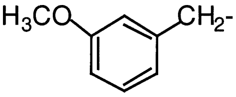
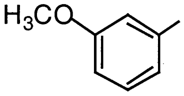
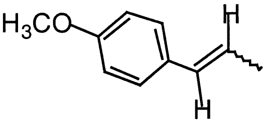
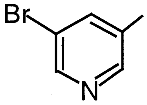
proximity of the ether and acid groups in **4e** may be responsible for the competing pathways. When 4 equiv. are used, methyl ether cleavage is no longer observed and yields increase dramatically. We speculate that with 4 equiv. of BCl_3, both the acid and ether are associated with boron-minimizing interaction, and the cleavage is no longer a competing reaction.

Table 1. Reaction of carboxylic acids **4a**–**g** with boron trichloride



(2)

Entry	R-	BCl_3 (eq)	Yield (%)
a		1	94
b		4	26
c		4	24
d		2	97
e		4	84
f		4	99
g		4	96

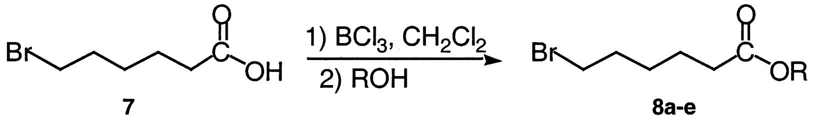
Substitution of other alcohols for methanol (Table 2) also results in esterification,[10] however, as the bulk of the alcohol increases the yield decreases. Primary alcohols form esters in good yield. Secondary and tertiary alcohols form esters, but the yields are not as high. Though it is not very efficient, *tert*-butyl alcohol affords the *tert*-butyl ester **8d**. Interestingly, the same reagent, boron trichloride, which cleaves benzyl esters,[7] also forms benzyl ester **8e**.

Within the context of benzyl ester cleavage, benzyl ester **8e** is cleaved with boron trichloride then quenched with methanol to yield the methyl ester **8a** (Scheme 2). This is a high-yielding transformation that is more versatile than simple esterification where concentration and removal of the undesired alcohol drives the equilibrium to the desired ester.

The tandem O–C bond cleavage and ester formation also forms amide **9** by using the same protocol but with ammonia quench instead of alcohol. This latter process and the formation of other acid derivatives is under investigation.

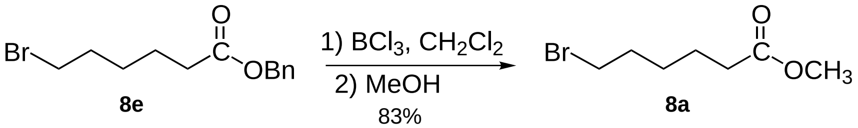
In summary, the ether and ester cleaving property of boron trichloride[5,7] is harnessed as a simple, generally efficient method for esterification. In addition, both cleavage and ester formation is effected sequentially in a one-pot process.

Table 2. Esterification of carboxylic acid **7** with varying alcohols



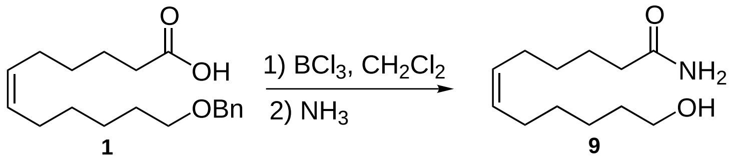
(3)

Entry	Alcohol	R	Yield (%)
a	MeOH	Me	97
b	EtOH	Et	60
c	*i*-PrOH	*i*-Pr	36
d	*t*-BuOH	*t*-Bu	25
e	BnOH	Bn	51



(4)

Scheme 2. *pseudo*-Transesterification of benzyl ester **8e**.



(5)

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10. **Reaction of 6-bromohexanoic acid (7) with boron trichloride**. To a stirred solution of 6-bromohexanoic acid (1.2043 g, 6.17 mmol) in dry CH_2Cl_2 (10 mL) at −78°C was added BCl_3 (1 M solution in CH_2Cl_2, 6.50 mL, 6.50 mmol). The clear solution was warmed to 0°C and stirred for 0.5 h. The reaction mixture was cooled to −78°C and excess methanol (3.00 mL, 74.06 mmol) was added via syringe. The solution was warmed to rt, then diluted with excess ether (25 mL) and washed subsequently with sat. Na_2CO_3 (50 mL), and brine (50 mL) then dried with $MgSO_4$. The excess solvents were removed under reduced pressure to give the methyl ester **4a** as an oil (97%). IR (neat): 2944, 2862, and 1739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40–1.59 (m, 2H), 1.61–1.69 (m, 2H), 1.81–1.90 (m, 2H), 2.31 (t, 2H, $J=8.75$ Hz), 3.39 (t, 2H, $J=6.97$ Hz), 3.65 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 24.3, 27.9, 32.6, 33.7, 34.0, 51.8, 174.1; m/e 210, 177, 74 (base), 59.