

## A Mild Protocol for the Conversion of Simple Esters to *tert*-Butyl Esters

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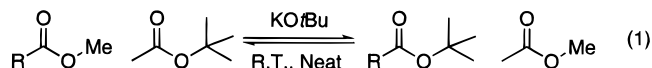
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### Introduction

The ester functional group is ubiquitous throughout the natural and synthetic world of organic chemistry and has resulted in decades of effort being devoted to its synthesis and manipulation. In addition to being valuable synthetic targets themselves, esters also serve the role of protective groups for other functionalities. Simple esters, however, are problematic in that harsh reaction conditions are normally required for net hydrolysis. To circumvent such undesirable reaction conditions, a number of alternative ester types have been presented which may be deprotected under mild, and oftentimes, orthogonal reaction conditions (e.g., acid,  $H_2$ -Pd/C,  $F^-$ ).<sup>1,2</sup> The *tert*-butyl ester has found a unique and desirable role in this scheme in that it can be converted to the carboxylic acid under mild acid conditions.

Recently, we reported on the ability of certain alkali-metal alkoxides to catalyze the ester-interchange reaction (eq 1).<sup>3</sup> The extremely rapid rates of reaction effected



by such catalysts ( $>10^6$  times more active than previously reported catalysts)<sup>4</sup> allow one to process *tert*-butyl esters at reasonable rates. The enhanced reactivity coupled with the low cost and commercial availability of catalyst solutions makes the ester-interchange reaction a viable alternative to transesterification-type processes.<sup>5</sup> We report herein the synthesis of a number of *tert*-butyl esters from their corresponding methyl or ethyl esters as a demonstration of the synthetic utility and viability of the catalyzed ester-interchange reaction.

### Results and Discussion

As a demonstration of the synthetic utility of the alkali-metal alkoxide cluster-catalyzed ester-interchange reaction, a number of simple esters were refunctionalized to the more useful *tert*-butyl ester using a commercial source of potassium *tert*-butoxide in THF as the catalyst (eq 1, Table 1). As shown in eq 1, the employed catalyst only equilibrates the esters, and so reaction conditions were developed wherein one product ester is volatile (methyl acetate) and is removed in vacuo to drive the reaction forward. Unfortunately *tert*-butyl acetate is also

volatile, resulting in an optimized protocol which requires several charges of this reagent (see Experimental Section).

This reaction has many attractive features including short reaction times, ambient temperature conditions, toleration of high substrate concentrations, and relatively low catalyst loadings,<sup>6</sup> the latter feature being especially significant in maintaining mild reaction conditions. The ability to push the reaction to high conversion ( $>98\%$ ) also simplifies workup to removing the catalyst by filtering through silica gel and concentrating in vacuo.<sup>7</sup> Alternatively, a standard aqueous workup (or pH 7 buffer) can be utilized which obviates the need for silica gel in the workup.

Optimization of reaction conditions led to the reported stepwise addition of 1 mol % KO<sup>t</sup>Bu (as a 1 M solution in THF) and 1 equiv of *tert*-butyl acetate under dynamic vacuum to remove the volatile methyl acetate.<sup>8,9</sup> Catalyst deactivation was observed to occur under low catalyst loadings and under single-addition conditions (addition of 8 mol % KO<sup>t</sup>Bu and 8 equiv of *tert*-butyl acetate to ethyl hydrocinnamate under dynamic vacuum leads to 24% conversion, cf. entry 1). Due to the difficulties we often encountered in separating products from starting esters, we recommend the stepwise approach which routinely gives  $>98\%$  conversion and high isolated yields, except as noted below.

The entries in Table 1 highlight the fact that both aromatic and aliphatic esters are good substrates for the interchange reaction. One of the criteria for this reaction protocol is that the starting ester be nonvolatile. Qualitatively, methyl benzoates containing electron-withdrawing groups (entries 2–5) are more reactive than those with electron-donating groups (entries 6–8), though the latter can easily be driven to high conversions. The exception to this observation is the *p*-nitro-substituted substrate which proceeded sluggishly and formed several unidentified byproducts. The noninnocence of this functionality presumably disrupts the structure of the active alkoxide cluster.<sup>3</sup> Also problematic were substrates containing acidic hetero functionalities such as methyl *p*-amino- and *p*-hydroxybenzoate which failed to give *tert*-butyl ester products (not shown), presumably due to competing deprotonation processes.

We ascribe the reduced and lack of reactivity of the substrates in entries 10 and 11, respectively, to the enhanced acidities of these esters. Since the  $-OPh$  ester is expected to be  $\sim 1.8$   $pK_a$  units more acidic than the  $-OMe$  ester, these substrates apparently represent a

(6) Since this reaction is entropically controlled (i.e.,  $\Delta H_{rxn} \sim 0$ ), no exotherms accompany large-scale reactions.

(7) It is imperative that all of the catalyst be completely inactivated on silica gel before washing with ethyl acetate as any remaining active catalyst will convert the product *tert*-butyl esters into ethyl esters.

(8) Aspirator vacuum often works well for reactive substrates but requires the use of an intermediate drying tube. More convenient, and utilized in the above experimental, was the use of a standard vacuum pump.

(9) Attempts to recycle the *tert*-butyl acetate using traps or condensers failed to improve the optimized conditions at the reported scales. Large-scale reactions may benefit from such an experimental setup.

(10) These estimates are based on the known  $pK_a$ 's of methoxyacetophenone (22.9) and phenoxyacetophenone (21.1) in DMSO; see: Bordwell, S. G.; Van Der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1885–1886.

(11) We estimate, on the basis of a  $pK_a$  value of 30.3 for *tert*-butyl acetate (DMSO), that the  $pK_a$  of the esters in entries 10 and 11 are 28.8 and 27.0, respectively.

(12) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463 and references therein.

(1) *Protective Groups In Organic Synthesis*, 2nd ed.; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley & Sons, Inc.: New York, 1991; pp 227–269.

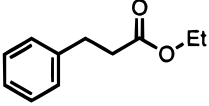
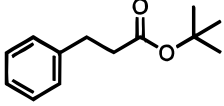
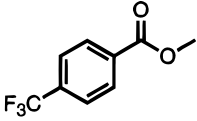
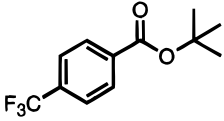
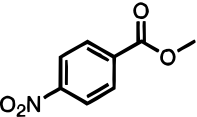
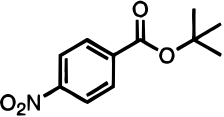
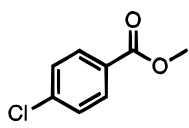
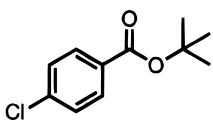
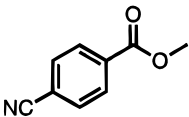
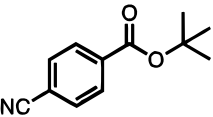
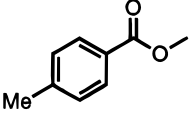
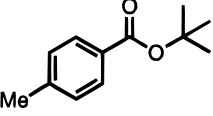
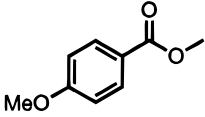
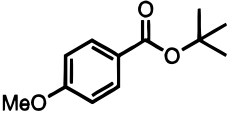
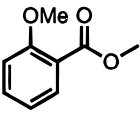
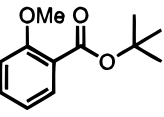
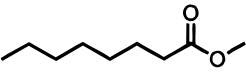
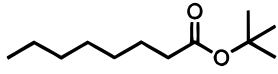
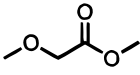
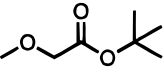
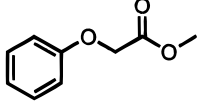
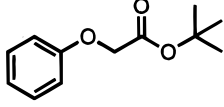
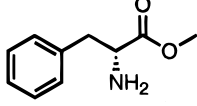
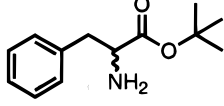
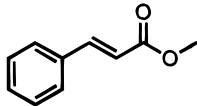
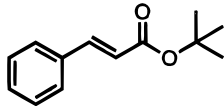
(2) For an alternative alkali-metal-catalyzed approach to the equilibration of esters and alcohols, see: (a) Rowan, S. J.; Hamilton, D. G.; Brady, P. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1997**, *119*, 2578–2579. (b) Brady, P. A.; Bonar-Law, R. P.; Rowan, S. J.; Suckling, C. J.; Sanders, J. K. M. *Chem. Commun.* **1996**, 319–320.

(3) Stanton, M. G.; Gagné, M. R. *J. Am. Chem. Soc.* **1997**, *119*, 5075–5076.

(4) Okanu, T.; Hayashizaki, Y.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1863–1865.

(5) For a recent review on the transesterification reaction, see: Otera, J. *Chem. Rev.* **1993**, *93*, 1449–1470.

Table 1. Synthesis of *tert*-Butyl Esters Using Catalytic Quantities of KO<sup>t</sup>Bu<sup>a</sup>

Entry	Ester	Product	mol % catalyst	equiv. <sup>t</sup> BuOAc	%Yield (%Conv.)
1			8	8	88(>98)
2			5	5	93(>99)
3			5	2	13(40)
4			6	5	99(>98)
5			6	5	92(>97)
6			6	5	96(>98)
7			6	5	98(98)
8			6	5	98(>98)
9			6	6	92(99)
10			10	5	---(25) <sup>b</sup>
11			5	5	---(<5)
12			5	5	95(>98) <sup>c</sup>
13			6	5	96(>98)

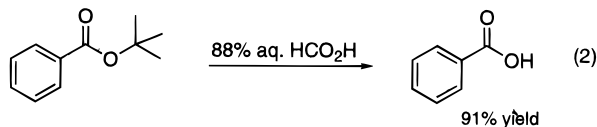
<sup>a</sup> See Experimental Section for details; yields represent isolated materials of >98% purity; conversions are determined by GC and are reported relative to starting material. <sup>b</sup> Reaction did not reach equilibrium (i.e., 1:1 ratio of product and substrate) even in the absence of vacuum. <sup>c</sup> Product was racemic by optical rotation.

lower limit for the  $pK_a$  of a viable substrate.<sup>10-12</sup> Amino acid esters (entry 12) can also be refunctionalized; however, the enhanced acidity of this functional group makes it susceptible to reversible enolization, and only racemic product is obtained. The interchange reaction

is also applicable to  $\alpha,\beta$ -unsaturated esters (entry 13) indicating that if 1,4-addition is competitive, it is reversible.

To confirm that *tert*-butyl esters can indeed be selectively deprotected under mild conditions, we exposed both

methyl and *tert*-butyl benzoate to aqueous formic acid reaction conditions. After 3 h the methyl ester did not react, while the *tert*-butyl ester was completely converted to benzoic acid and isolated in 91% yield (eq 2).<sup>13</sup> The conversion of a methyl ester to a *tert*-butyl ester followed by formic acid deprotection thus provides a high-yield two-step procedure for hydrolyzing simple esters under mild conditions.



### Conclusion

We provide herein an experimentally simple protocol for the conversion of methyl and ethyl esters to valuable *tert*-butyl ester products in high yields and purity with minimal workup requirements. The process utilizes the recently discovered ability of alkali-metal alkoxide clusters to catalyze the ester-interchange reaction rapidly and under mild conditions. We hope that this will provide the general synthetic community with a new route for the synthesis of these useful compounds.

### Experimental Section

**Materials and Methods.** Esters were purchased from Aldrich and distilled over CaH<sub>2</sub>. Potassium *tert*-butoxide solutions (1 M in THF) were purchased from Aldrich and used fresh. Reactions were carried out in inert nitrogen atmosphere using standard Schlenk line techniques.

(13) *tert*-Butyl benzoate (10 mmol) was treated with 20 mL of 88% formic acid solution at 25 °C for 3 h.

**General Procedure for the Synthesis of *tert*-Butyl Esters.** The methyl ester (10 mmol) and *tert*-butyl acetate (10 mmol, 1.35 mL) were combined in a 50-mL Schlenk flask. To this mixture of liquids was added potassium *tert*-butoxide (1 mol %, 0.1 mmol, 0.1 mL of a 1 M solution in THF) via syringe. The reaction vessel was stirred under dynamic vacuum at room temperature for 5 min to remove methyl acetate and then backfilled with nitrogen. An additional equivalent of *tert*-butyl acetate (1.35 mL) and 1 mol % catalyst were added, and the above procedure was repeated until the conversion of the methyl ester to the *tert*-butyl ester was >98% by GC. The total amount of catalyst required to achieve this degree of conversion for each substrate is reported in Table 1. The catalyst was removed by passing the reaction mixture through a plug of silica gel and washing with THF followed by ethyl acetate.<sup>7</sup> The eluent was then evaporated to dryness in vacuo to yield the corresponding *tert*-butyl ester. All isolated materials except the product in entry 2 are known compounds and were shown to be pure by both <sup>1</sup>H NMR and GC.

Alternatively, the reaction solutions were diluted with 20 mL of diethyl ether and the reactions quenched with 10 mL of water or pH 7 buffer solution. The organic fractions were then washed with 10 mL of brine and dried over MgSO<sub>4</sub>, and the solutions were concentrated in vacuo to yield the desired products.

**Characterization of *tert*-butyl 4-(trifluoromethyl)benzoate:** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.07 (d, *J* = 8 Hz, 2H), 7.64 (d, *J* = 8 Hz, 2H), 1.58 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 164.4, 135.2, 133.9 (q, *J*<sub>C-F</sub> = 32.5 Hz), 129.8, 125.1 (br), 123.7 (q, *J*<sub>C-F</sub> = 273 Hz), 81.8, 28.0; <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ -65.4 (s); FT-IR (neat on KBr, cm<sup>-1</sup>) 1709 (s), 1160 (vs), 1121 (vs).

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