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AN IMPROVED PROTOCOL FOR THE PREPARATION OF 2,6-DI(*tert*-BUTYL)-4-METHYLPHENYL (BHT) ALKANOATES

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Abstract: *Treatment of the acid chloride derivatives* ***2a-e*** *with potassium 2,6-di(*tert*-butyl)-4-methyl phenoxide* ***1b*** *afforded the corresponding BHT esters* ***3a-e*** *in 83–95% yield.*

Hindered aryl esters have considerable utility in the promotion of a variety of electrophilic and nucleophilic reactions.[1,2,3] This is due primarily to their inherent resistance to hydrolysis *via* nucleophilic acyl substitution.[2] They therefore represent an important functional group in organic chemistry and have enjoyed widespread application to a range of synthetic problems.[4] The most noteworthy of these are aldol condensation reactions,[1] *in situ* ketene acetal formation,[2] and conjugate additions to α,β-unsaturated esters.[3] To date, only one method has emerged for their preparation, which utilizes the lithium phenoxide **1a** with the corresponding acid chlorides **2** affording the BHT esters **3** in reasonable yields (**Scheme 1**).[2] Excellent yields of the esters have been reported, however, they require a large excess of the acid chloride which is very often the expensive component of the reaction.[5]

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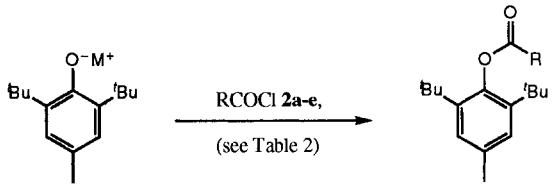
Scheme 1



1a M = Li
b M = K

3a-e

In this letter we report an improved method for the preparation of BHT esters, which employs the potassium rather than the lithium phenoxide ion (see Table 1). In the course of our synthetic studies we required the preparation of the BHT ester **3b**. However, initial attempts at repeating the published procedure on a *reduced reaction scale*, gave the ester **3b** in a reduced 66% yield (Entry 1). Increasing the amount of acid chloride also failed to give any significant increase in the yield (Entry 2). The reaction was then heated at reflux in order to increase the rate of reaction and thus drive it to completion, furnishing the BHT ester **3b** in a further reduced 58% yield (Entry 3). Increasing the amount of phenoxide ion also proved futile, giving the ester **3b** in a disappointing 56% yield (Entry 4). However, when the phenoxide metal ion was changed from lithium to potassium, the BHT ester **3b** was obtained in 83% yield (Entry 5).

Table 1: Optimization of BHT ester Formation with Acid Chloride **2b**

Entry	BHT (eq.)[a]	Base (equiv.)	Acid Chloride **2b** (eq.)	Temp[b]	Yield (%)[c]
1	1.00	^{n}BuLi (1.00)	1.05	RT	66
2	1.00	^{n}BuLi (1.00)	1.1	RT	67
3	1.00	^{n}BuLi (1.00)	1.1	Δ	58
4	1.25	^{n}BuLi (1.25)	1.0	RT	56
5	1.00	KHMDS (1.05)	1.1	RT	83

[a] Reactions were carried out on a 1-2 mmol scale. [b] Reactions were all stirred for 24 h. [c] Isolated yields.

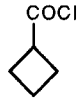
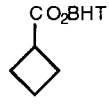
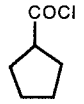
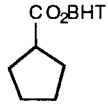
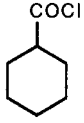
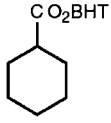
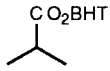
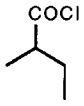
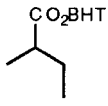
The dramatic increase was attributed to the harder, more ionic phenoxide ion **1b**. The validity of this was proven by making a direct comparison of the new protocol with that for known BHT esters which utilize the lithium phenoxide ion.[2] The potassium phenoxide **1b** was generally prepared on a 10 mmol scale at 0 °C and the freshly distilled acid chloride added directly. The extended reaction times originally reported were also found not to be necessary, with the optimum reaction time usually being overnight or *ca.* 12 hours.[2] If the reaction was worked up prematurely after (*ca.* 2 hours) there was, however, a significant drop in the yield.

The reaction was found to be reasonably sensitive to scale, with slightly lower yields being obtained on a reduced 1 mmol reaction scale. However, the yields were still superior to the lithium based protocol. Table 2 summarizes the results of our comparison study which clearly illustrates a significant increase in the yield for all the examples, except for isobutyryl chloride **2d** (Entry 4). The most impressive improvement was for 2-methylbutyryl chloride **2e** which gave a 27% increase in the yield (Entry 5).

In conclusion, the new protocol for the preparation of hindered aryl esters described herein should find general utility, especially in cases where the acid chloride is in short supply or is particularly expensive.

General Procedure for the Formation of BHT esters. Potassium bis(trimethylsilyl)amide solution (18.9 ml, 9.45 mmol; 0.5 M soln. in toluene, ex. Aldrich Chemical Co.) was added dropwise to a mechanically stirred, ice cooled, solution of 2,6-di(*tert*-butyl)-4-methyl phenol (1.983 g, 9.0 mmol) in anhydrous THF (9.0 ml) under an atmosphere of nitrogen.[6] The resulting cream colored phenoxide suspension was allowed to form at 0 °C for 30 minutes. Cyclohexane carbonyl chloride (1.3 ml, 9.9 mmol, 1.1 eq, freshly distilled) was added dropwise and the mixture allowed to warm to room temperature, within 5 minutes the reaction mixture became a homogeneous light yellow solution which was stirred for *ca.* 12 hours. The reaction mixture was then poured into saturated NH_4Cl solution (20 ml) shaken and the organic layer separated. The aqueous layer was then back extracted with dichloromethane (2 x 15 ml), and the combined organic layers were washed with saturated $NaHCO_3$ solution (20 ml) followed by saturated NaCl solution (20 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*

Table 2: Comparison of the Lithium *vs* Potassium Phenoxide ion Mediated Esterification

Entry	Acid Chloride[a]	Product[b]	**1a** (M = Li)[c]	**1b** (M = K)[d,e]
1	 **2a**	 **3a**	74	88
2	 **2b**	 **3b**	76	95
3	 **2c**	 **3c**	85	94
4	 **2d**	 **3d**	82	83
5	 **2e**	 **3e**	63	90

[a] Reactions were carried out with 1.1 equivalents of freshly distilled acid chlorides. [b] All products were identical with authentic samples by ^{1}NMR, IR and mp. [c] Ref. 2. [d] Reactions were carried out on a 10 mmol scale at room temperature for *ca.* 12 hours. [e] Isolated yields.

to afford a crude oil. Purification by flash chromatography on silica gel, eluting with hexane/dichloromethane (10 : 1, 4 : 1 and 1 : 1) furnished the BHT ester **3c** (2.781 g, 94%) as a white crystalline solid.

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6. The potassium phenoxide ion **1b** is fairly insoluble under the reaction conditions and requires efficient stirring on an increased reaction scale. The reaction often failed upon scale-up if the solution was not mechanically stirred.

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