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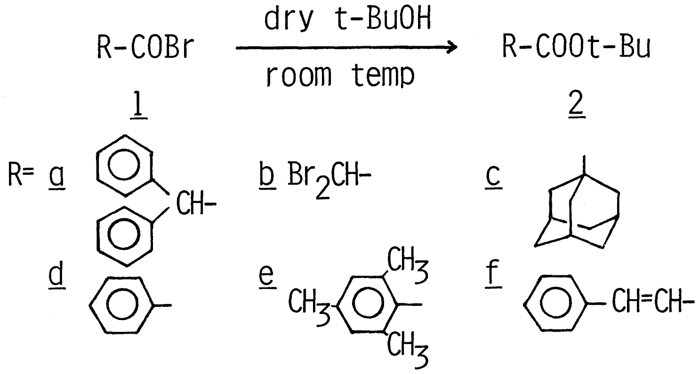
Activated Basic Alumina Promotes a Mild, Clean and High-Yield Racemization-Free Synthesis of t-Butyl Esters from Chiral Acid Bromides and t-Butyl Alcohol

Kazuo NAGASAWA,* Keiko OHHASHI, Asami YAMASHITA, and Keiichi ITO
Hokkaido Institute of Pharmaceutical Sciences,
7-1 Katsuraoka-cho, Otaru 047-02

Esterification of a variety of acid bromides having even steric bulkiness with t-BuOH/activated basic alumina gave the corresponding t-butyl esters in good to excellent yields. In the case of chiral acid bromides, no racemization has been ascertained for the first time.

Despite a wide selection of procedures for the carboxylic t-butyl ester synthesis,[1] there exist several limitations such as the necessity to use highly toxic[2] and/or inconvenient[3] to handle reagents, rigorous conditions,[4] tedious manipulations,[5] narrow range of applicability,[6] some of which may become critical, particularly in the complete chirality-retention esterification.[7] Therefore the new and reliable methods for their synthesis are still required. Generally, employing the chiral acyl halides with a hydrogen-bearing asymmetric α-carbon in a base-induced esterification with alcohols might be foolhardy since Cardellina[8] reported the quite easy racemization of (R)-(-)-phenylbutyryl chloride in the presence of pyridine and/or 4-dimethylaminopyridine(DMAP) at room temperature. Due to their exceptionally high reactivities and esterification-reliability,[8] however, we dared to give a challenge to an acylation of t-butyl alcohol with chiral and achiral acyl bromides in the presence of activated basic alumina.[9] As a result, surprisingly, no racemization was found and in addition, the otherwise inaccessible or poor-yield accessible t-butyl esters like 2c and 2e were acquired without any problems. Thus, we



now describe an efficient and mild racemization-free synthesis of carboxylic t-butyl esters for the first time.

Table 1. Comparison of the Effect of Inorganic and Organic Bases in the Conversion of 1a to 2a[a)]

Promoter	Solvent	Reaction Time/h	Isolated Yield of 2a/%
Activated Al_2O_3	dry C_6H_6	2	50
		9	96[b)]
Out-of-the-bottle Al_2O_3	dry C_6H_6	9	50
N,N-Dimethylaniline[c)]	dry ether	9	60
Pyridine[c)]	dry ether	9	55
t-BuOLi[d)]	dry THF	9	<20

a) For the reaction conditions, see a typical procedure.
b) Other solvents like ether and dichloromethane caused less acceptable yields of the t-butyl ester. c) Ref.1a. d) Ref. 5.

As shown in Table 1, activated basic alumina was found to suppress the HBr-induced decomposition of the product most effectively, giving an excellent yield of the corresponding t-butyl ester when diphenylacetyl bromide, 1a was treated, for comparison, with the typical bases such as basic alumina, dimethylaniline, pyridine and lithium t-butoxide, while the only marginal and disappointing yields were acquired with other bases.

Then, the combination of the activated basic alumina in dry benzene was expanded to several other acyl bromides[10)] to give the quite high yields of the products as depicted in Table 2, so the steric or electronic effects appear not to be in operation at least in our method. Moreover,the unprec-

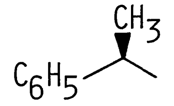
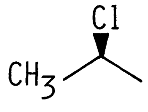
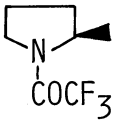
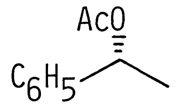
Table 2. Activated Basic Alumina-Promoted Synthesis of t-Butyl Esters[a)]

Product	Isolated Yield/%	bp/°C (Lit. bp/°C) mp	n_D^{20}	IR $\nu_{cm^{-1}}^{neat}$	^{1}H- and ^{13}C-NMR $\delta_{ppm}^{CDCl_3}$	
				-COOt-Bu	-COOt-Bu	-COOt-Bu
2a	96	82-83 (n-hexane)	——	1725	1.43	171.44
2b	84	85-86/11 Torr[b)]	1.4805	1740	1.52	163.56
2c	89	45-46 (n-hexane)	——	1730	1.55	169.95
2d	92	54/1 Torr (88-90/3 Torr)[c)]	1.4918	1725	1.45	168.95
2e	88	91/1 Torr	1.4926	1720	1.60	169.56
2f	90	96/1 Torr (144/8 Torr)[c)]	1.5377	1690	1.51	168.91

a) For the reaction conditions, see a typical procedure. b) 1 Torr=133.322 Pa. c) Ref. 5.

edented application to four representative chiral acyl bromides carrying a greatly racemization-labile hydrogen at an α asymmetric carbon was performed in order to verify the generality and mechanism of this method. As seen in Table 3, except only for an insufficient yield(25%) of (S)-(+)-acetyl mandelic acid t-butyl ester, it is very exciting and beyond belief that all the t-butyl esters obtained were evidenced to be enantiomerically pure by a chiral shift NMR inspection, indicating not through the readily producible ketene intermediates from the respective chiral acid bromides in marked contrast to some racemization(7-15%) with pyridine.11) Thus, our reaction system(acyl bromide/t-BuOH/activated basic alumina/dry benzene) offers a sterling alternative to the currently existing methods for a general carboxylic t-butyl ester synthesis.

Table 3. Chiral Acid Bromides and the Corresponding t-Butyl Esters a)

	R-COBr			R-COOt-Bu b)		
R	Isolated Yield/%	bp/°C n_D^{20}	$[\alpha]_D^{20}$ (CH_2Cl_2)	Isolated Yield/%	bp/°C n_D^{20}	$[\alpha]_D^{20}$ (CH_2Cl_2)
	94	77/2 Torr c) 1.5520	-31.2° (c=1.23)	91	68/1 Torr 1.4796	-30.7° d) (c=1.096)
	75	27/9 Torr 1.4830	-16.0° (c=1.076)	75	48/15 Torr 1.4184	+16.6° d) (c=1.056)
	90	100/1 Torr 1.4622	-79.1° (c=1.33)	90	80/1 Torr 1.4209	-67.0° (c=1.048)
	90	oil 1.5386	+95.0° (c=1.05)	25	oil 1.4802	+65.1° d) (c=1)

a) For the reaction conditions, see a typical procedure. b) Chiral shift NMR inspection with $Eu(hfc)_3$ or $Pr(hfc)_3$ revealed none of the opposite enantiomer, showing enantiomerically pure. c) 1 Torr=133.322 Pa. d) In place of activated basic alumina, some racemization (7-15%) was found to occur with pyridine.

In closing, activated basic alumina obtained easily from the commercial one is of much practical value particularly for a large-scale operation of carboxylic t-butyl esters and recovered alumina can be recycled.12) In addition, manipulation is quite simple and even the crude products after an easy work-up can be employed for further applications because of high purity. Still more startling, optically pure carboxylic t-butyl esters can be prepared, for the first time, from the chiral acid bromides with a hydrogen-carrying asymmetric α-carbon under the basic reaction conditions.

In a typical procedure, (R)-(-)-2-phenylpropionyl bromide(12.8 g,0.06 mol) obtained from the parent acid and oxalyl bromide, in dry benzene(150 ml) was added with stirring to a suspension of activated basic alumina(60 g) given by heating the commercial one(200 mesh, Alumina(activated), Wako Chemical Co. Ltd.) at 500 °C/1 Torr for 15 h, in dry benzene containing dry t-BuOH(22.3 g, 0.3 mol). After a violent 9-h stirring of the whole at room temperature under argon, alumina was filtered off and thoroughly washed with dichloromethane(50 ml) and the combined organic layer was dried ($MgSO_4$), evaporated, and distilled, giving a 91% yield of (R)-(-)-t-butyl 2-phenylpropionate, for -$\underline{C}$OOt-Bu IR(neat) 1730 cm^{-1}, ^{13}C-NMR($CDCl_3$) 173.84 ppm.

Further application and the scope by using our reagent combination are now being under way.

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10) By an acid chloride method (Ref. 6e), all the t-butyl esters listed in Table 2 were produced by a prolonged reaction time (>50 h) and in worthless (traces) yields. Comparison between both the methods will be reported elsewhere in full detail.

11) The greater extent of racemization (ca. 30%) took place as expected when the more basic 4-dimethylaminopyridine (DMAP) was utilized.

12) Recovered alumina in the text can be used repeatedly by rinsing them with methanol-water (95:5) several times and by drying at 60-70 °C in an oven.

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