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Transesterifications mediated by *t*-BuNH$_2$

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Abstract

A mild protocol for transesterification of simple esters is described. The method is based on the use of *t*-BuNH$_2$/ROH (R = Me, Et, *i*-Pr, *t*-Bu) with or without LiBr. The scope of the procedure was explored for aliphatic and aromatic esters. The protocol is particularly useful when going from higher to lower hindered esters and harsh reaction conditions are needed for the reversal process. A rationalization of the mechanism is presented. The scope and limitation of this transformation are also described.

Keywords: Transesterification; *tert*-Butylamine; Lithium bromide; Aliphatic esters; Aromatic esters

The ester formation is an important and commonly used transformation in organic synthesis, in industrial as well as in academic laboratories. Esters are some of the most common functional groups in organic transformations, playing an important role in synthetic chemistry serving as key intermediates or protecting groups in the multiple-step synthesis of many natural products.[1] Ester syntheses are generally accomplished either from coupling of carboxylic acids with alcohols in a variety of conditions[2] and/or by transesterification of an ester with an alcohol (alcoholysis).[1,2b,3] For alcoholysis, a number of useful and reliable procedures catalyzed by a variety of protic and Lewis acids, organic and inorganic bases, enzymes and antibodies have been developed.[3,4] The alkoxy groups commonly used in the new ester formation are methoxy, ethoxy, *t*-butoxy, allyloxy and benzyloxy groups,[1,4a,b,5] and less frequently *i*-propoxy,[6] and prenyloxy[7] groups. Even though numerous methods of transesterification have been reported in the literature including variation and improvements of well established procedures there is still a constant need to discover and apply new protocols, which require mild conditions especially for compounds with acid and base sensitive functionalities.

In the course of our studies on the use of *t*-BuNH$_2$/MeOH mediated deprotection of carbamates,[8] we found that esters suffer rapid transesterification in the presence of this base. A number of organic bases, for example, Et$_3$N, 2-(dimethylamino)ethanol (DMAE) and Et$_3$N/DMF have been used for transesterifications in peptide-(polystyrene resin) cleavage[9a–c] and in the synthesis of artificial β-sheets.[9d] The diamino alcohol 2-{[2(dimethylamino)ethyl]methylamino}ethanol (DAEMAE) has been used for transesterification of glycidyl methylacrylate.[10a,b] *N*,*N*-Dimethyltrimethylenediamine (DMTMD), 4-methylpiperidine (4-MP), Et$_2$NH and tetramethyldiaminoethane (TEMED) have been used in biodiesel-transesterification of biological oils.[11] The more complex bases benzoylquinine (BQ) and a thiourea-amine system have been used in the preparation of β-amino acids[12a] and for selective transesterification of lactide.[12b] *N*,*N*-Diethylaminopropylated silica gel (NDEAP)[13a] and 4-(*N*,*N*-dimethylamino)pyridine (DMAP)[1] have been used for transesterification of β-ketoesters. DMAP has also been used for transesterification of trihaloethyl esters.[13b] DBU has been used for transesterification of *p*-nitrophenyl phosphonates[14a] and the DBU/LiBr system[14b] has been used for

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transesterification of simple esters and peptides. The latest author claims that no reaction occurs in the absence of LiBr. More recently, amino hemiacetals/hemiketals have been used for transesterification of *p*-nitrophenyl esters.[15] As can be seen, a number of organic bases are used in transesterifications; however, the main drawback of most of them is their narrow range of applicability. Here we wish to report our results on a systematic investigation involving the soft nucleophile *t*-$BuNH_2$/ROH (R = Me, Et, *i*-Pr, *t*-Bu, Bn) system as an efficient promoter for transesterification. We also found that significant improvements in reaction times can be achieved by including lithium bromide (LiBr) in the transesterification.

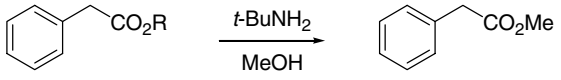
We initially investigated the transesterification reaction using phenyl acetates **1a**–**d**. As indicated in Table 1 excellent yields have been achieved including reactions involving sterically hindered esters. In a typical experimental procedure, ester **1a** was refluxed for 8 h with MeOH in the presence of 5 equiv of *t*-$BuNH_2$ (entry 1). The reaction progress was monitored by TLC and/or ^{1}H NMR analysis and after completion the excess *t*-$BuNH_2$/MeOH mixture was removed from the reaction simply by evaporation under vacuum or by fractional distillation to recover *t*-$BuNH_2$. The procedure gave the desired methyl ester **2** in very high yield and neither column chromatography nor aqueous work-up was necessary to afford pure ester **2**. Although the reaction proceeds well with only 1 equiv of *t*-$BuNH_2$, the reaction is quite slow. Under similar conditions esters **1b** and **1c** afforded product **2** in quantitative yield but they needed harsh reaction conditions, that is, high temperature and pressure (entries 4 and 6).

The reaction times for the conversion of **1a** into **2** were substantially reduced when an excess of the amine was used (entries 2 and 3). Accordingly, we decided to use as an optimum reaction conditions 20 equiv of *t*-$BuNH_2$. Under these reaction conditions the transesterification of **1a**–**c** into **2** was completed in 2, 21, and 2 h, respectively (entries 3, 5, and 7). In the case of **1d** (entry 8) only 15% of **2** was observed in the ^{1}H NMR spectrum of the reaction crude. As is shown in Table 1 the steric effect of the alkoxy group of esters **1a**–**d** influences the rate of transesterification in the order OEt ≈ OBn > O*i*-Pr ≫ O*t*-Bu.

To ensure that *t*-$BuNH_2$ facilitated the transesterification process, ester **1a** was heated under reflux of MeOH in the absence of the base but no ester **2** was detected even under forcing conditions after 24 h of reaction (entry 9). The result of this experiment confirmed that the alcohol alone does not directly provide the alkoxyl group for transesterification and *t*-$BuNH_2$ is indeed necessary for this transformation.

On the basis of these results, we decided to pursue the use of *t*-$BuNH_2$/MeOH system together with LiBr for further transesterification. Remarkably, stirring **1a** with 20 equiv of *t*-$BuNH_2$ and 5 equiv of LiBr at room temperature for 3 h led to homologue **2** in quantitative yield (entry 10). Encouraged by this result, we screened the reaction of

Table 1
t-$BuNH_2$ transesterification with MeOH



1a-d **2**

Entry	Compound	Equiv of LiBr	Equiv of *t*-$BuNH_2$	Reaction conditions	Time (h)	Yield (%)
1	**1a**: R = Et	—	5	Reflux	8	Quant
2	**1a**	—	15	Reflux	3	Quant
3	**1a**	—	20	Reflux	2	Quant
4	**1b**: R = *i*-Pr	—	5	Sealed tube	175	Quant
5	**1b**	—	20	Reflux	21	Quant
6	**1c**: R = Bn	—	5	Sealed tube	24	Quant
7	**1c**	—	20	Reflux	2	Quant
8	**1d**: R = *t*-Bu	—	20	Reflux	35	15[a]
9	**1a**	—	—	Reflux	24	—
10	**1a**	5	20	rt	3	Quant
11	**1a**	5	5	rt	13	98
12	**1a**	5	1	rt	15	98
13	**1a**	1	1	rt	25	Quant
14	**1a**	5	5	Reflux	1	99
15	**1a**	5	1	Reflux	4	Quant
16	**1a**	1	1	Reflux	8	Quant
17	**1a**	5	—	Reflux	24	29[a]
18	**1a**	5	5 mL	Reflux	24	—[b]
19	**1b**	5	5	Reflux	32	99
20	**1c**	5	5	Reflux	0.25	Quant
21	**1d**	5	5	Sealed tube	39	20[a]

[a] Calculated by ^{1}H NMR analysis of the crude material.
[b] The reaction was carried out without MeOH.

1a varying the equivalents of *t*-$BuNH_2$, LiBr, and reaction time (entries 11–16). As indicated in entries 10-13, reducing the amounts of LiBr or *t*-$BuNH_2$ still afforded excellent yields of **2** albeit in longer reaction times. With the objective of achieving high conversion in short reaction time, we further explore the transesterification under reflux (entries 14–16). The best reaction conditions for the transformation of **1a** into **2**, namely in the presence of 5 equiv of *t*-$BuNH_2$ and 5 equiv of LiBr under reflux, occurred in 1 h (entry 14).

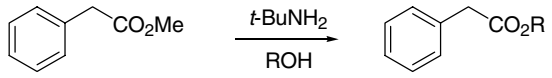
Compound **1a** was also utilized in a control experiment to assess the role of LiBr and reveal its participation in the observed increased rate of transesterification. The reaction occurred with LiBr/MeOH in the absence of *t*-$BuNH_2$ but only with 29% yield after 24 h (entry 17). On the other hand, the reaction of **1a** with LiBr/*t*-$BuNH_2$ in the absence of MeOH (entry 18) did not produce the corresponding amide even in traces as judged by a careful ^1H NMR spectral analysis of the crude material. These results indicate that for the reaction to proceed faster the *t*-$BuNH_2$ and MeOH must be present in the reaction mixture and Li^+ should activate the carbonyl ester group to improve base catalyzed O-nucleophilic attack by the MeOH.[16] Despite the greater nucleophilicity of *t*-$BuNH_2$ relative to MeOH,[17] steric hindrance in this base should prevent nucleophilic attack at the carbonyl ester group.

More sterically congested esters **1b–d** (entries 19–21) were also found to react under these conditions to afford **2** in excellent yields. In the cases of **1b** and **1d** longer reaction times were necessary and for **1d** harsh reaction conditions were also required.

Methyl phenyl acetate (**2**) underwent transesterification to higher homologues with *t*-$BuNH_2$, EtOH, and *i*-PrOH to afford the corresponding esters **1a** and **1b** (Table 2, entries 1 and 2). As is shown in Table 2, methyl ester **2** required fairly harsh reaction conditions to undergo transesterification to higher homologues. When *t*-$BuNH_2$/alcohol/LiBr system was used, better results were obtained. Thus, reactions carried out under reflux afforded esters **1a** and **1b** in excellent yields (entries 4–6). Ester **1d** was not obtained either in the absence or presence of LiBr even under longer reaction times (entries 3 and 7).

We next turn our attention on the transesterification of aromatic esters **3a–c** (Table 3). The reactions are very clean

Table 2
t-$BuNH_2$ transesterification with EtOH, *i*-PrOH, and *t*-BuOH

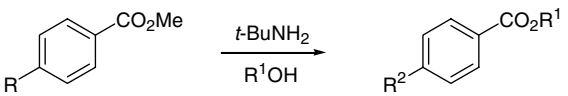


2 **1a-d**

Entry	Equiv of LiBr	Equiv of *t*-$BuNH_2$	Reaction conditions	Time (h)	Product	Yield (%)
1	—	20	Reflux	24	**1a**: R = Et	66[b]
2	—	20	Sealed tube	24	**1b**: R = *i*-Pr	6[b]
3	—	20	Sealed tube	24	**1d**: R = *t*-Bu	—[a]
4	5	5	Reflux	6	**1a**	Quant
5	5	5	Reflux	32	**1b**	77[b]
6	5	15	Reflux	33	**1b**	99
7	5	5	Reflux	24	**1d**	—[a]

[a] Starting material was recovered.
[b] Calculated by ^1H NMR analysis of the crude material.

Table 3
t-$BuNH_2$ transesterification of aromatic esters



3a-c **4a-e**

Entry[a]	Compound	Equiv of LiBr	Reaction conditions	Time (h)	Product	Yield (%)
1	**3a**: R = H	—	Reflux	46	**4a**: R^1 = Et, R^2 = H	33[a,c]
2	**3b**: R = $N(Me)_2$	—	Reflux	24	**4b**: R^1 = Et, R^2 = $N(Me)_2$	—[a]
3	**3c**: R = NO_2	—	Reflux	10	**4c**: R^1 = Et, R^2 = NO_2	Quant[a]
4	**3c**	—	Reflux	34	**4d**: R^1 = *i*-Pr, R^2 = NO_2	55[a,c]
5	**3c**	—	Sealed tube	32	**4e**: R^1 = *t*-Bu, R^2 = NO_2	—[a]
6	**3c**	5	Reflux	1	**4c**	99[b]
7	**3c**	5	Reflux	11	**4d**	96[b]

[a] Reactions were carried out with 20 equiv of *t*-$BuNH_2$.
[b] Reactions were carried out with 5 equiv of *t*-$BuNH_2$.
[c] Calculated by ^1H NMR analysis of the crude material.

and also gave very high yields. The presence of an electron donating group retards the reaction rate, while the presence of an electron withdrawing group does the contrary, as it is evident in entries 2 and 3. These results, together with those obtained by the treatment of **1** or **2** with different alcohols (Tables 1 and 2), clearly indicate that these esters undergo direct nucleophilic attack at the carbonyl ester group by the corresponding alkoxide.

In conclusion, the present procedure using *t*-$BuNH_2$/alcohol/LiBr provides an interesting example for transesterification. Various types of carboxylic esters including aliphatic and aromatic compounds have been subjected to transesterification using a variety of alcohols according to this procedure.[18] The reactions are, in general, very clean and give very high yields. Besides, the simplicity of this approach and the low cost of the reagents enhance its attractiveness. The method is especially well applicable when going from higher to lower hindered esters but harsh reaction conditions are needed for the reversal process. Works on other reactions catalyzed by *t*-$BuNH_2$/MeOH are currently underway in our laboratory.

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18. *Typical experimental procedure*:
To the appropriate ester (0.6 mmol) in the corresponding alcohol (5 mL) was added *t*-$BuNH_2$ (20 equiv, 1.26 mL) or *t*-$BuNH_2$ (5 equiv, 0.315 mL)/LiBr (5 equiv, 0.261 g), and the mixture was stirred under reflux for the appropriate time (Tables). After complete conversion, as indicated by TLC or ^{1}H NMR spectroscopy, the volatile reagents were evaporated to afford the pure transesterified product in the case of esters treated only with *t*-$BuNH_2$/ROH. For esters treated with *t*-$BuNH_2$/ROH/LiBr the residue was diluted with EtOAc (50 mL), washed with saturated aqueous NH_4Cl solution (2 × 15 mL), dried over anhydrous Na_2SO_4 and evaporated to give the pure transesterified product.
The identity and the purity of the reaction products were established by their ^{1}H NMR data by direct comparison with authentic samples.