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High-pressure transesterification of sterically hindered esters

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ABSTRACT

A mild, rapid, and efficient method for the solvolysis of sterically hindered esters under high pressure is described. Transesterification is carried out in the presence of DBU at room temperature and at a pressure of 10 kbar to give quantitative conversions within short reaction times. The substrates examined included aromatic and aliphatic esters of sterically hindered alcohols and phenols. An optically pure benzyl ester of phenylalanine was chosen to study racemization of the amino acid esters under high-pressure reaction conditions.

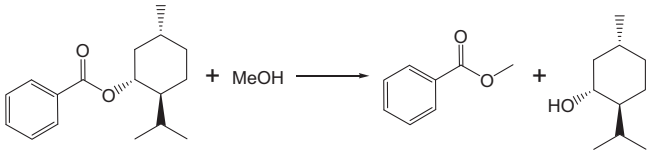
Transesterification is of significant importance in organic synthesis as an equivalent of mild ester hydrolysis. This reaction is well known and presents numerous preparative approaches.[1–4] However, its application to sterically hindered esters is limited, because traditional methods require harsh reaction conditions when applied to such substrates. This prevents its use in certain cases where it would be a natural solution. One such example is the cleavage of *tert*-butyl protecting groups from esters. The regular procedure requires acidic conditions, which make it unsuitable for acid-sensitive compounds. A frequently used alternative protection for esters are 2,6-dialkylphenyl groups. Their removal requires the use of hot aqueous solutions of sodium hydroxide or solutions of sodium methoxide in a mixture of toluene and hexamethylphosphoramide.[5,6]

Efficient cleavage of sterically hindered esters is also desired in syntheses involving alcohol-type chiral auxiliaries, such as menthol, borneol, and their derivatives. Near quantitative removal would allow recycling of most of the auxiliaries. Additionally, the chemical correlation method relies on the quantitative cleavage to determine the obtained diastereomeric excesses.[7]

Many sterols are viable candidates as starting materials and chiral pool compounds because of their natural abundance. However, some are only available in acylated form, which usually necessitates their transformation into the free alcohol form. Acylated forms of sterols are also obtained in the later stages of multi-step syntheses where the intended product is the free alcohol. Conventional methods for ester cleavage and earlier proposed high-pressure hydrolysis methods are not satisfactory in those cases.[8]

These examples indicate that a mild and efficient method for cleavage of sterically hindered esters would solve many existing synthetic problems. Both kinetic data (volume of activation ca. 12 cm^3) and our earlier experience suggested that base-catalyzed high-pressure transesterification might be such a method.[9] Moreover, in the literature, there are several patents involving high-pressure approaches to transesterifications.[10,11]

Table 1
Optimization of the reaction



Base	Amount (equiv)	Pressure (kbar)	Time (h)	Yield (%)
None	—	10	16	0
Et_3N	0.1	3	16	0
Et_3N	0.1	10	16	6
Et_3N	15	10	2	65
DBU	0.2	3	16	27
DBU	0.2	10	16	46
DBU	0.75	10	16	65
DBU	1	10	16	85
DBU	1	10	1	22
DBU	1	10	2	65
DBU	2	10	1	38
DBU	2	10	2	98[a]

[a] 100% conversion.

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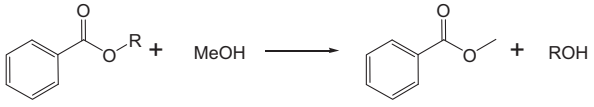
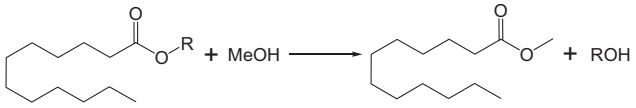
Table 2
Scope of the reaction of benzoyl esters under the optimized conditions (2 equiv DBU, 2 h)



Substrate	Yield (%)
2,6-Dimethylphenyl benzoate	95
2,6-Diisopropylphenyl benzoate	97
2-*tert*-Butylphenyl benzoate	98
tert-Butyl benzoate	97
Menthyl benzoate	98
Bornyl benzoate	98
neo-Pentyl benzoate	97

Table 3
Scope of the reaction of lauroyl esters



Substrate	Time (h)	DBU (equiv)	Yield (%)
2,6-Dimethylphenyl laurate	2	2	98
2,6-Diisopropylphenyl laurate	3.5	2	96
2-*tert*-Butylphenyl laurate	2	2	98
tert-Butyl laurate	2	2	98
Menthyl laurate	2	2	67
Menthyl laurate	2	3	76
Bornyl laurate	2	2	72
Bornyl laurate	2	3	94

Table 4
Reaction of menthyl benzoate with other alcohols

Alcohol	Solvent	Yield (%)
Methanol	Methanol	98
Ethanol	Ethanol	75
Propan-1-ol	Propan-1-ol	15
Trifluoroethanol	Trifluoroethanol	0
Propan-2-ol	Propan-2-ol	0
tert-Butanol (5 equiv)	Dichloromethane	0

During the optimization study, menthyl benzoate was chosen as the model compound due to the frequent use of menthol derivatives as chiral auxiliaries and its bulkiness. Four parameters were investigated: type and amount of amine catalyst, pressure and duration of the reaction. The reactions were conducted in methanol, which at the same time acted as the transesterifying agent. Two commonly used Lewis bases chosen were: triethylamine (Et_3N) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

In the initial series of reactions, DBU appeared to be the more efficient catalyst. The degree of conversion was found to increase with pressure and time. Reaction time and economical considerations suggested that further trials should be conducted under 10 kbar pressure, since this pressure afforded good conversions while still being achievable in most commercial high-pressure equipment. The optimal reaction conditions for the model compound were 10 kbar pressure, 2 equiv of DBU, and a reaction time of 2 h.[12] The use of excess of the amine enabled quantitative conversions while maintaining short reaction times. In all cases, the yields are based on the methyl esters formed. The results of the optimization studies are shown in Table 1.

Next, 12 other sterically hindered esters were examined. The results for the reaction of benzoic esters are summarized in Table 2. In all cases, the reactions proceeded with quantitative conversions.

Esters of lauric acids were also examined. For substrates giving unsatisfactory conversions under the optimized conditions, additional reactions with larger excesses of DBU or longer reaction times were performed; for detailed results, see Table 3.

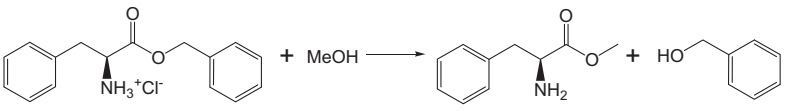
In base-catalyzed transesterifications, an alkoxide ion attacks the acyl group, therefore, bulky alkoxide ions should react less readily due to the larger energy of activation required. Table 4 lists the results obtained by varying the transesterifying agent in the reaction with menthyl benzoate under the optimized conditions. The results were in accordance with expectations.

To verify the advantages of the proposed method, two comparative reactions with the model compound were performed. The first used the conditions described by Seebach et al. (2 equiv DBU, 8 equiv LiCl, rt).[13] However, the reaction was incomplete even after 7 days. The second involved using the optimized conditions, but heating under reflux instead of high pressure. There was only minor progress in the reaction after 20 h. Therefore we conclude that the new approach is a substantial improvement over existing methods.

In order to check if racemization took place, L-phenylalanine benzyl ester was selected as a substrate for transesterification. An additional equivalent of DBU compared to the optimal conditions was added to neutralize the hydrochloride salt of L-phenylalanine benzyl ester. Quantitative conversions were achieved in each case and it was found that, after 2 h, the obtained methyl ester of phenylalanine was only slightly racemized (95% ee). Elongation of the reaction time caused additional racemization, but reduction of the DBU loading led to phenylalanine methyl ester with 99% ee in 78% yield (Table 5).[14]

In summary, we have demonstrated that high pressure transesterification represents a mild, rapid, and efficient method for hydrolysis of sterically hindered esters. We have shown the

Table 5
Phenylalanine benzyl ester transesterification



Time (h)	DBU (equiv)	ee (%)
16	3	59
2	3	95
2	2	97
2	1.5	98
2	1.1	99

versatility of this transformation by applying the method to both aromatic and aliphatic esters of a variety of sterically hindered alcohols and phenols. We have also revealed that the method can be used for optically active amino acid esters without leading to racemization.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.094. These data include MOL files and InChiKeys of the most important compounds described in this article.

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12. General procedure for the transesterification: 0.4 mmol of ester and 0.8 mmol of DBU were placed in a 2 ml PTFE ampoule, filled with methanol, closed, and transferred to a high-pressure vessel. The pressure was then slowly raised to 10 kbar at room temperature. After 2 h the chamber was decompressed. The reaction mixture was concentrated under reduced pressure and the residue was separated using flash column chromatography (SiO_2; hexane/AcOEt in various proportions). All products were analyzed by NMR spectroscopy and the spectra were consistent with the structures of the desired products.
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14. The enantiomeric excess of phenylalanine methyl ester, after being derivatized to *N*-benzyloxycarbonyl phenylalanine methyl ester with benzyl chloroformate and diisopropylethylamine in CH_2Cl_2 at room temperature, was determined using a Chiralcel-OD column, with 10:90 2-PrOH/hexane as eluent, temp 25 °C, 1.0 mL/min flow rate, and 210 nm detection wavelength.