



Lipase-catalyzed amidation of carboxylic acid and amines

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ABSTRACT

The amidation reaction is of a very particular interest, especially in the pharmaceutical industry and always requires the activation of the acid with a large excess of reactants. Therefore, a large amount of waste is generated. In order to reduce the environmental impact of such reaction, we have developed enzymatic amidation conditions which are compatible with a wide range of amines and acids, in particular with the biologically relevant lipoic acid. Water is the only by-product generated during this reaction thus a very high atom economy is obtained. In addition, we have shown that the lipase can be recovered and reused several times without a significant loss of activity.

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The amide bond is one of the most widespread bonds since it is the core structure of peptides and proteins. Nature assembles enzymatically the free aminoacids in the ribosome. However, synthetic chemists have devised the use of alternative methods since the reaction of a free carboxylic acid and a free amine (as in the case of free aminoacids) will solely results in the formation of the ammonium carboxylate salt, obtained from the acid-base reaction, unless elevated temperature is applied.¹ (See Scheme 1).

For peptides and proteins formation, the use of protected aminoacids and a rather expensive activator or the immobilization on a resin, allowing the use of large excess of reagents, are key parameters for a successful synthesis and are routinely applied.² However, the amide bond formation avoiding poor atom economy or large excess of reagents has been identified as a priority by the ACS Green Chemistry Institute and by pharmaceutical companies.³ Therefore, new sustainable methods for the formation of amide bonds are of high concern. In the recent years several methods have been developed for the acylation of amines with free carboxylic acids.¹ Probably one of the most versatile methods rely on the use of boronic acids which transiently generates an activated acid.⁴ These Lewis acids, which activity can be finely tuned by modifying the substituents at the boron atom, usually have a high functional group tolerance and are stable in the presence of water. However, the

water generated in the course of the reaction has to be removed and usually elevated temperatures are required to achieve good yields, which conditions can also lead to racemization.

Transition metal catalysts, especially elements from group IV (Ti, Zr, Hf), have been used on several occurrence since the simultaneous seminal work of Williams and Adolfsson.^{5,1c} The same drawbacks (water removal and high temperature) can also be pointed out. Very recently, diphenylsilane has been used stoichiometrically for the direct coupling of carboxylic acid and amines in refluxing acetonitrile.⁶

Enzymes, especially lipases, have been used for a long time to perform esterification reactions using the alcohol as solvent to draw the equilibrium towards the formation of the ester. When both a primary or secondary amine and an alcohol (which is typically used as solvent) are present in the reaction medium, the ester formed is ultimately converted to the corresponding amide.⁷ The direct conversion of a carboxylic acid and an amine remains scarce in the literature,⁸ or limited to specific substrates such as the formation of primary amides from various sources of ammonia.⁹

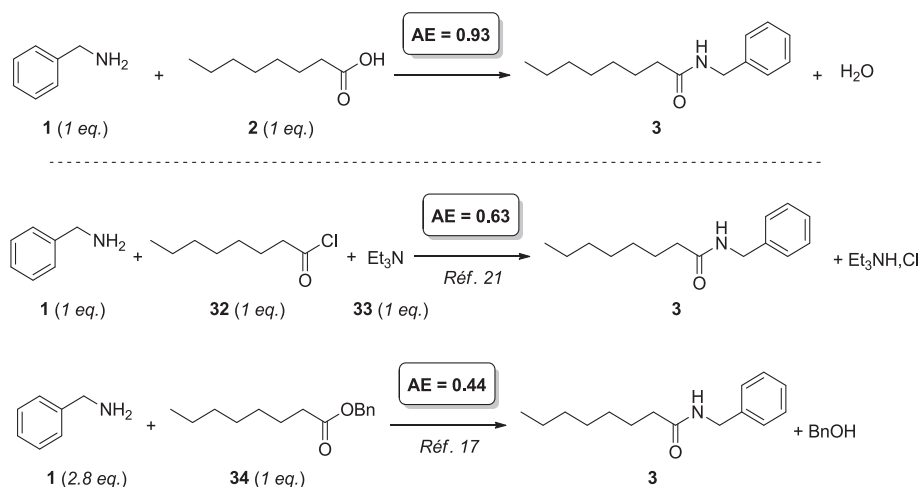
Discussion

We wish to report here a simple and convenient method for the direct amidation of free carboxylic acids and amines without the transient formation of an active ester, generating therefore water as the sole, non-toxic, by-product.

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Scheme 1. Atom economy.

Solvent screening

We initially started our investigations of the lipase catalyzed amidation reaction in various solvents with octanoic acid and benzyl amine.¹⁰ Immobilized *Candida Antarctica* Lipase B (CAL-B) was chosen for its ability to perform several kinds of organic reaction and for its compatibility with organic solvents.¹¹ The reaction was carried out at 50 °C with molecular sieves to avoid the reversible hydrolysis reaction. For all the reactions described throughout this paper a control reaction without lipase was performed in order to assess the lipase amidation activity under various conditions. It is well-known that the solvent can have a dramatic influence on the outcome of a biocatalyzed reaction.¹² Indeed, the solvent should be able to solubilize the reactants as well as the product and stabilize the intermediates involved, but it can also change the conformation of the active site or drain out the water molecules from it, thus modifying the catalytic properties of the enzymes.

Although lipases are known to perform better in apolar solvents,¹³ we have screened usual organic solvents such as toluene or well tolerated etheral solvent like 1,4-dioxane, MTBE, diglyme and cyclopentyl methyl ether CPME¹⁴ in order to ensure solubilization of the reactants or the product and to avoid heterogeneous conditions.

We have also screened greener or safer alternatives (MeTHF, propylene carbonate, PEG200) and the ionic liquid BMP(NTf₂).¹⁵

These different types of solvents allow us to screen various polarities and proticities thus selecting the best solvent. In most of the solvents the yields were very satisfactory (Table 1: entries 1–7), above 80%, which proves the versatility of this enzyme in organic solvents. Interestingly, the reaction performed in Butyl Methyl Pyrrolidinium Triflimide (BMP(NTf₂)) only afford the desired compound in 28% yield. This result is rather surprising since CAL-B has been for amidation with ammonia in ionic liquids,¹⁶ or used in a Baeyer-Villiger oxidation in BMP(NTf₂)¹⁷ with good results.

In order to rationalize the influence of the solvent we have initially examined the dielectric constant (ϵ , Table 1) and the dipole moment (μ , Table) of these solvents. It turns out that the solvents with a dielectric constant below 12.5 (except pyridine) afford yields above 80%. A similar trend can be drawn with the dipole moment, which best yields are obtained with the less polar solvents (<2 Debye). We have then examined the solvatochromic parameters of these solvents and another trend can be drawn. Yields over 80% are achieved with solvents having hydrogen-bond acidity (α) of 0 (pyridine excluded) whereas the hydrogen-bond basicity (β) doesn't seem to have an influence. However the polarity/polarizability parameter (π^*) needs to remain below 0.65. Similar observation has been made for the E_T^N parameter which has to be under 0.25 to give the best yields (*t*-BuOH excluded).

Considering other criterions such as the ability to dissolve a wider range of substrates or the price we have decided to use

Table 1
Solvent screening.

Entry	Solvent	Yield	ϵ	μ (D)	π^*	α	β	E_T^N
1	1,4-dioxane	94%	2,21	0,45	0,55	0	0,37	0,164
2	Toluene	92%	2,38	0,31	0,54	0	0,11	0,099
3	MeTHF	89%	7,53	1,38	0,48	0	0,45	0,179
4	CPME	89%	4,76	1,27	0,42	0	0,53	–
5	<i>t</i> -BuOH	83%	12,5	1,66	0,41	0,68	0,93	0,389
6	MTBE	83%	2,6	1,32	–	0	–	0,124
7	Diglyme	80%	7,3	1,92	0,64	0	–	0,244
8	Propylene Carbonate	73%	65,5	4,94	0,83	0	0,4	0,472
9	Acetone	33%	20,7	2,69	0,71	0,08	0,48	0,355
10	Acetonitrile	23%	37,5	3,44	0,75	0,19	0,31	0,460
11	BMP(NTf ₂)	28%	–	–	0,95	0,41	0,723	0,540
12	PEG 200	50%	18,35	–	–	–	–	–
13	Pyridine	4%	12,4	2,37	0,87	0	0,64	0,302
14	1,4-dioxane*	87%	–	–	–	–	–	–
15	1,4-dioxane/H ₂ O (10:1)*	25%	–	–	–	–	–	–

* No MS 3 Å was used

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