$LiNTf_2$-Catalyzed Aminolysis of Lactones with Stoichiometric Quantities of Amines

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Abstract: $LiNTf_2$ in the reaction of lactones with amines is able to activate cyclic esters towards ring opening, thus leading to clean open-chain amides under mild conditions and using a stoichiometric amount of amine. The generality of the method was demonstrated by a range of selected lactones and amines.

Key words: amides, ring opening, Lewis acids, lactones, catalysis

Lactone aminolysis is a common transformation which allows direct conversion into the corresponding amides, and it is a highly attractive transformation in modern organic synthesis, although it generally requires harsh conditions,[1] which are limiting factors especially in scale-up procedures. Moreover, excess of amine is generally used to guarantee proper conversion and reaction rate, making the direct aminolysis not feasible especially when the amines are not readily available.[2] Several methods have been reported in the literature for facilitating the reaction of lactones with amines,[3] and the use of the Weinreb reagents coming from the reaction of trimethylaluminium with an amine, or the use of 2-hydroxypyridine have been considered as being the most popular.[4] Recently, Shimizu et al. reported on the use of Me_2AlCl–HN(OMe)Me as an efficient amidating agent.[5]

As lactone aminolysis is commonly carried out in multistep synthesis, there is an interest for versatile activators which could be of great benefit, especially where stoichiometric amounts of valuable building blocks have to be used. Recently, Cossy et al. reported the application of $LiNTf_2$ as an efficient activator towards regioselective ring opening of epoxides with a variety of nucleophiles including amines.[6] This process was adopted by our group as a tool to synthesize intermediate compounds on the gram scale.[7] We reasoned that a similar effect could exist with respect to oxygen atoms of lactones, as a consequence of activation of the carbonyl group towards nucleophilic aminolysis, thus opening the route towards a general and facile method for the ring opening of lactones of different ring size with amines belonging to different classes. Specifically, as a part of a program towards the development of heterocycles carrying chemical diversity, we were interested in finding an easy and efficient method for synthesizing molecules through the aminolysis of lactones,[8] and in particular we were interested in achieving the reaction using stoichiometric quantities of the reactants. After the initial observation that the addition of substoichiometric quantities of $LiNTF_2$ could catalyze the aminolysis of γ-butyrolactone (**1**), we started investigating the best conditions to achieve optimal conversion using allylamine (Figure 1), specifically by tuning the solvent and the temperature, and monitoring the reaction time until completion.

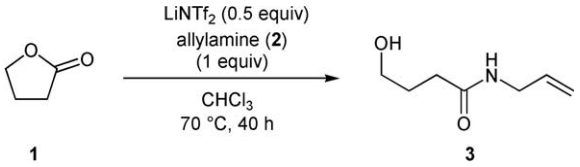

Figure 1

Among the three main solvent systems tested, namely THF, EtOH, and chloroform, the corresponding control experiments were also carried out at refluxing temperatures, to have reference data on the yields in the absence of $LiNTF_2$ (Table 1, entries 1–4). Reactions conducted in EtOH at 95 °C in a sealed vial showed 43% and 62% yields after 17 hours and 40 hours, respectively (Table 1), whereas THF and chloroform produced the title amido alcohol in 37% and 52% yields, respectively. Addition of $LiNTF_2$ in THF did not lead to any improvement (entry 5), as the reaction outcome dropped to 12%, indicating that this solvent was not compatible with the lithium salt catalyzed aminolysis. The reaction in EtOH and in the presence of $LiNTF_2$ indicated a small effect of the catalyst, as a similar yield as the control experiment was achieved at lower temperature (Table 1, entry 6 vs. entry 2). We next turned our attention to halogenated solvents, as these were reported being the systems of choice in the aminolysis of epoxides,[6] probably due to their low coordinating effect towards the catalyst, thus resulting in a lower interference in the process. Dichloromethane was tested at different temperatures, giving at 40 °C yields similar to EtOH, with no additional improvement observed on prolonging the reaction time from 17 hours to 72 hours (entries 7–9). Also, the addition of 10% 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) produced the same result as that in pure dichloromethane, indicating no beneficial effect to the reaction

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(entry 10). These preliminary experiments suggested that the solvent plays a role in the reaction, and that an aprotic solvent with a high polar character might allow the lithium salt to work optimally in activating the carbonyl group towards the ring-opening aminolysis. In fact, chloroform showed a marked improvement with respect to dichloromethane when the reaction was carried out at reflux temperature and the yield was raised to 83% (entry 12). Finally, the best conditions were achieved by prolonged reaction of γ-butyrolactone and allylamine in stoichiometric amounts, in chloroform at 85 °C for 40 hours, giving a clean product in quantitative yield (entry 13).[9] Further attempts to lower both the temperature and the catalyst load resulted in lower yield (entries 14–16). Whenever an incomplete reaction was observed, the crude mixture contained only the starting material and the title product, without significant amount of degraded material.

Table 1 Aminolysis of γ-Butyrolactone with Allylamine (1 equiv) in a Sealed Vial

Entry	Solvent	Temp (°C)	Reaction time (h)	$LiNTf_2$ (equiv)	Yield (%)
1	THF	85[a]	24	0	37
2	EtOH	95[a]	17	0	43
3	EtOH	95[a]	40	0	62
4	$CHCl_3$	85[a]	40	0	52
5	THF	50	17	0.5	12
6	EtOH	50	17	0.5	62
7	CH_2Cl_2	20	17	0.5	33
8	CH_2Cl_2	40	17	0.5	58
9	CH_2Cl_2	40	72	0.5	60
10	CH_2Cl_2–HFIP (9:1)	20	17	0.5	38
11	$ClCH_2CH_2Cl$	20	17	0.5	48
12	$CHCl_3$	85[a]	17	0.5	83
13	**$CHCl_3$**	**85[a]**	**40**	**0.5**	**99**
14	$CHCl_3$	20	17	0.5	43
15	$CHCl_3$	85[a]	40	0.2	62
16	$CHCl_3$	85[a]	40	0.1	60

[a] Oil-bath temperature corresponding to reflux condition in the sealed vial.

As a hypothesized mechanism relating to the activating role of $LiNTf_2$ towards lactone aminolysis, the coordinating effect of the lactone carbonyl group was considered. Thus, the interaction of the strong electron-withdrawing lithium salt with the C=O bond would increase the electrophilic character of the carbonyl carbon atom towards nucleophilic addition of the amine, thus resulting in higher yield of the corresponding hydroxyamide.

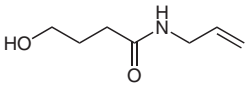
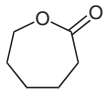
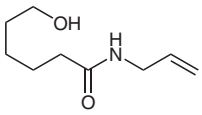
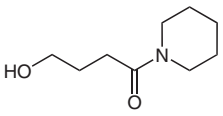
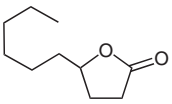
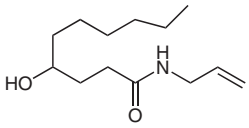
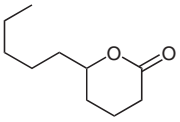
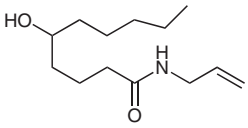
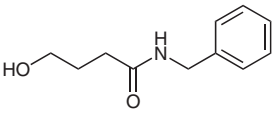
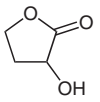
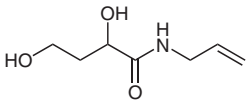
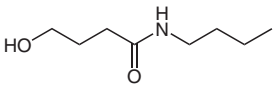
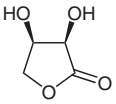
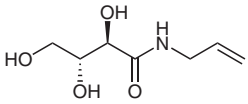
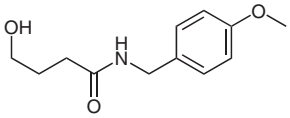
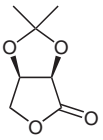
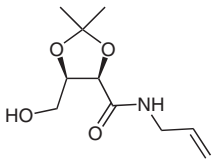
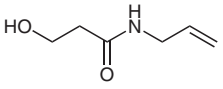
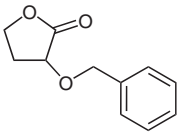
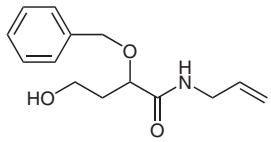
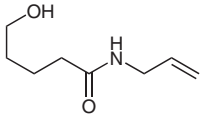
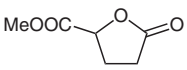
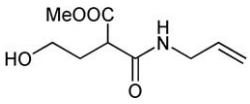
We next investigated the generality of the process by performing the reaction with lactones varying in ring size and in substitution pattern, and also using amines of different steric and nucleophilic characters. Ring opening of γ-butyrolactones was explored with secondary amines, and while piperidine gave quantitative yield, the bulky diisopropylamine did not yield any product, suggesting the relevance of steric hindrance (Table 2, entries 2 and 3). Also, the nucleophilic character of the amine influenced the reaction conversion, as benzylamine and butylamine gave 100% yield, whereas aromatic *p*-anisidine gave the adduct in only 11% yield and the corresponding lactam resulting from subsequent cyclization of the hydroxyamide in 12% yield (entry 6).

Surveying the ring size of lactones indicated that the reactions of 4–6-membered rings proceeded in almost quantitative yields, and that ε-caprolactone reacted under these conditions to furnish the corresponding product in 53% yield (Table 2, entries 7–9). The presence of unprotected functional groups, and in particular of hydroxyl functions, proved to influence negatively the outcome of the reaction (entries 12 and 13), probably by interfering with the lithium salt. In particular, unprotected erythronolactone **20** failed to react, giving the adduct in only 6% yield, whereas the corresponding isopropylidene derivative **22**, having the two hydroxyls embedded in the dioxolane ring, reacted cleanly to produce the adduct in 93% yield (entries 13 and 14, respectively). Similarly, α-benzyloxy-γ-butyrolactone (**24**) reacted quantitatively, compared to the corresponding unprotected α-hydroxy-γ-butyrolactone (**18**), which furnished the amido alcohol in 46% yield (entries 15 and 12, respectively), thus corroborating the importance of having protic functional groups protected. In all cases, the amides resulting from aminolysis of the corresponding lactones were easily purified by standard flash chromatography.

Finally, preliminary investigations indicated that this catalytic system worked with even more unactivated carboxylic esters, as the amidation of Boc-Ala-OMe with allylamine in the presence of 0.5 equivalent of $LiNTf_2$ under standard conditions furnished the corresponding Boc-alanine allylamide in 52% yield, whereas only the starting reagents were obtained in the corresponding control experiment without the lithium salt. Similar results were obtained for the synthesis of protected hydroxamic acids from lactones, as the reaction of γ-butyrolactone with *O*-benzylhydroxylamine resulted in 45% yield under standard conditions compared to 0% yield in the control experiment, thus indicating the possibility of preparing *N*-hydroxamic acids from lactones by this method.

In conclusion, we have reported a mild and effective method for the aminolysis of lactones with stoichiometric quantities of amines, which consists of the use of $LiNTf_2$ as an activator of the carbonyl function of the lactone. The method was developed using chloroform as solvent, and the generality of the reaction was demonstrated with selected amines and lactones, indicating the importance of avoiding steric hindrance and of the protection of protic

Table 2 Reaction f Various Lactones with Amines

Entry	Amine	Lactone	Product	Yield (%)	Entry	Amine	Lactone	Product	Yield (%)
1	allylamine (**2**)	 **1**	 **3**	99	9	**2**	 **12**	 **13**	53
2	piperidine	**1**	 **4**	100	10	**2**	 **14**	 **15**	80
3	diisopropy-lamine	**1**	–	0	11	**2**	 **16**	 **17**	64
4	benzylamine	**1**	 **5**	100	12	**2**	 **18**	 **19**	46
5	butylamine	**1**	 **6**	99	13	**2**	 **20**	 **21**	6
6	*p*-methoxy-benzylamine	**1**	 **7**	11[a]	14	**2**	 **22**	 **23**	93
7	**2**	 **8**	 **9**	100	15	**2**	 **24**	 **25**	99
8	**2**	 **10**	 **11**	5	16	**2**	 **26**	 **27**	80

[a] The corresponding butyrolactam was also obtained in 12% yield.

functional groups for optimal conversions. The method was also tested for the reaction of allylamine with the methyl ester of Boc-alanine, and for the lactone aminolysis of γ-butyrolactone with protected hydroxylamine, indicating the possibility of a more general application of LiNTf$_2$-catalyzed reactions of lactones and esters.

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(9) **General Procedure for Lactone Aminolysis; Synthesis of *N*-Allyl-4-hydroxybutyramide(3)**: To a solution of γ-butyrolactone (**1**; 1 equiv) and allylamine (**2**; 1 equiv) in anhyd $CHCl_3$ (0.5 mL/mmol) was added under a nitrogen atmosphere $LiNTf_2$ (0.5 equiv). The mixture was stirred in a sealed vial at 85 °C (oil bath) for 40 h, then it was washed with a sat. $NaHCO_3$ solution, and the organic phase was evaporated to give the title product as a clean viscous oil (99%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.62 (br, 1 H, NH), 5.73–6.03 (m, 1 H, =CH), 5.04–5.23 (m, 2 H, $=CH_2$), 4.02 (br, 1 H, OH), 3.88 (t, *J* = 5.5 Hz, 2 H), 3.72 (t, *J* = 5.5 Hz, 2 H), 2.40 (t, *J* = 6.2 Hz, 2 H), 1.79–1.96 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.2 (s, C=O), 137.1 (d, =CH), 119.4 (t, $=CH_2$), 65.1 (t, CH_2), 45.4 (t, CH_2), 36.4 (t, CH_2), 31.5 (t, CH_2). MS (EI, 70 eV): *m*/*z* (%) = 143 (1) [M^+], 99 (28), 84 (10), 69 (14), 57 (100). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.70; H, 9.14; N, 9.76.