Pergamon

Tetrahedron Letters 42 (2001) 2439–2441

TETRAHEDRON LETTERS

A mild method for ring-opening aminolysis of lactones

Wenming Liu, David D. Xu,* Oljan Repič and Thomas J. Blacklock

Process R & D, Chemical and Analytical Development, Novartis Institute for Biomedical Research, 59 Route 10, East Hanover, NJ 07936, USA

Received 5 October 2000; revised 15 January 2001; accepted 30 January 2001

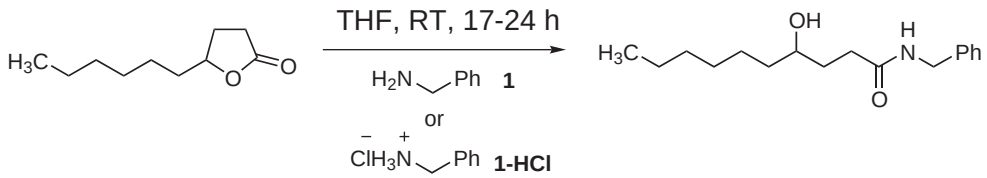
Abstract—A mild and general method for lactone aminolysis is reported. Sodium 2-ethylhexanoate (NaEH) is found to serve both as a base and a catalyst in aminolysis of a variety of lactones by benzylamine hydrochloride. The nearly neutral pH conditions make this method applicable to many acid/base sensitive substrates.

Lactone aminolysis, apparently a simple transformation, generally requires rather harsh conditions, such as high temperature[1] or strong alkali–metal catalysts.[2] These conditions pose significant limitations to their applications. Furthermore, a large excess of amines is frequently used to ensure proper conversion and reaction rate,[3] making the direct aminolysis uneconomical especially when the amines are not readily available.

Recently, we encountered a challenging aminolysis of a sugar-derived lactone by a primary amine: both the amine and the lactone were products of expensive multi-step syntheses. Additionally, the lactone was unstable at slightly elevated pHs and the amine could not be easily isolated in its free base form. In search for neutral and mild conditions to carry out this lactone aminolysis and the possibility of utilizing the amine HCl salt directly, we came upon an earlier report from our group.[4] Prasad et al. reported that sodium 2-ethylhexanoate (NaEH) can be used as an effective organic-soluble acid scavenger in amine acylations with acid chloride. We found that, in addition to being an effective acid scavenger, NaEH also offered a dramatic accelerating effect for lactone aminolysis by the HCl salts of primary amines.

The catalytic effect of NaEH in lactone aminolysis is clearly demonstrated in using benzylamine and γ-decanolactone as the model system (Table 1). No aminolysis was observed when γ-decanolactone was treated with benzylamine at ambient temperature in tetrahydrofuran (entry 1). Triethylamine showed no

Table 1. Aminolysis of γ-decanolactone with benzylamine or benzylamine hydrochloride



Entry	Reactant	Additive (equiv)	Yield (%)[a]
1	**1**	None	0
2	**1**	Et_3N (2.5)	0
3	***1-HCl***	*Et_3N (2.5)*	*0*
4	**1**	NaEH (2.5)	10
5	***1-HCl***	*NaEH (2.5)*	*83*

[a] Isolated yields.

Keywords: lactone; aminolysis; sodium 2-ethylhexanoate.

* Corresponding author. E-mail: david.xu@pharma.novartis.com

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00196-4

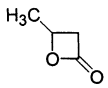
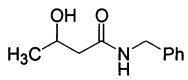
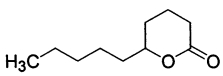
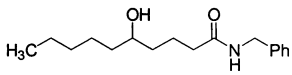
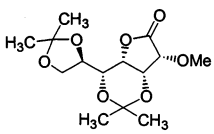
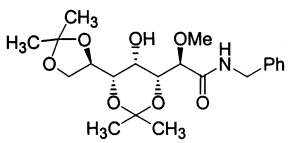
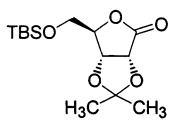
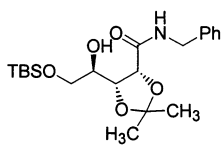
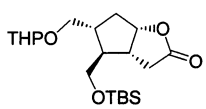
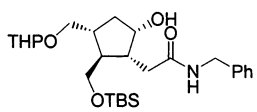
observable effect on the aminolysis when either the free base or the HCl salt of benzylamine was used (entries 2 and 3). On the other hand, NaEH demonstrated small but discernible catalytic effect when free benzylamine was used, as indicated by the 10% isolated yield of the product amide (entry 4). However, NaEH showed a dramatic catalytic effect when benzylamine hydrochloride was used directly, the product amide was isolated in 83% yield (entry 5)!

The general applicability of this lactone aminolysis method is demonstrated in Table 2. A variety of structurally distinct lactones were successfully converted to the corresponding amides by benzylamine hydrochloride in the presence of NaEH. Compared with γ-lactone, β- and δ-lactones were much more reactive under these conditions (entries 1 and 2). The mildness of our method was demonstrated by the aminolysis of **4a**, which was shown to be both acid and base sensitive. It readily underwent β-elimination under basic conditions, while the acetonide protecting group rearranged from 1,2- to 1,3-dioxane under acidic conditions. Our conditions effected the formation of amide **4b** smoothly at ambient temperature without any noticeable decomposition of **4a** or the scrambling of the acetonide protecting group (entry 3). Similarly, lactone **5a** with a TBS and an acetonide protecting group was converted to its benzyl amide in excellent yield (entry 4). The sterically hindered bicyclic lactone **6a** failed to give the product amide at room temperature (entry 5), but the desired amide **6b** could be generated in good yield after the reaction was heated at 70°C for 8 h (entry 6). Both tetrahydropyranyl and *t*-butyldimethylsilyl protecting groups remained intact under these conditions, again demonstrating the mildness of this aminolysis method.

While our limited data do not allow us to offer a definitive mechanism for the significant accelerating effect of NaEH in lactone aminolysis, we speculate that the acceleration arises from concerted actions of the base (NaEH) and its conjugated acid (EHA) on both the amine and the lactone.[5] We are currently in the process of elucidating the mechanism of this reaction and utilizing this method to other examples.

In summary, a mild and general lactone aminolysis method is presented. NaEH has been shown to significantly accelerate the aminolysis of lactones with the HCl salts of primary amines. The conditions are close

Table 2. Lactone aminolysis with benzylamine hydrochloride (1.5 equiv.) and NaEH (2.5 equiv.) in tetrahydrofuran[a]

Entry	Lactone	Reaction temp.(°C)	Time (h)	Product[b]	Yield[c] (%)
1	 **2a**	23	4	 **2b**	97
2	 **3a**	23	4	 **3b**	91
3	 **4a**	23	12	 **4b**	79
4	 **5a**	23	12	 **5b**	90
5	 **6a**	23	12	 **6b**	trace
6	**6a**	70	8	**6b**	78

[a] The reaction was carried out following the general procedure described in the notes.[6]
[b] All products were fully characterized by spectroscopic methods.
[c] Isolated yields.

to neutral and compatible with a variety of acid/base sensitive substrates.

Acknowledgements

We would like to thank Drs. Kapa Prasad and Liladhar Waykole for helpful discussions.

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6. **General procedure**: To the mixture of lactone **4a** (1.0 mmol), benzylamine hydrochloride (1.5 mmol), and NaEH (2.5 mmol) under nitrogen was charged THF (5 mL), then the reaction mixture was stirred at room temperature for 12 h. After the lactone was consumed, 5 mL of saturated sodium chloride aqueous solution and 10 mL of ethyl acetate were added. The two layers were separated, the aqueous layer was back-extracted with another 10 mL of ethyl acetate. Combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was separated by chromatography (EtOAc/hexane) to afford the product **4b**: mp 167–169°C; $[\alpha]_D^{25}$ +25.2 (*c* 1.3, MeOH); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.38 (m, 5H), 6.82 (m, 1H), 4.53 (d, 2H, $J=6.0$ Hz), 4.30 (m, 1H), 4.17 (dd, 1H, $J=4.8$, 1.3 Hz), 4.09 (dd, 1H, $J=8.6$, 6.3 Hz), 3.98 (d, 1H, $J=4.8$ Hz), 3.89 (dd, 1H, $J=8.7$, 4.6 Hz), 3.80 (s, 1H), 3.63 (dd, 1H, $J=8.2$, 1.1 Hz), 3.53 (s, 3H), 1.43 (s, 3H), 1.42 (s, 6H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 138.3, 129.0, 128.0, 127.9, 109.6, 99.9, 83.0, 74.5, 73.7, 73.3, 67.4, 63.4, 60.1, 43.5, 29.7, 27.3, 25.5, 19.5; MS *m*/*z* 432 $(M+Na)^+$, 410 (MH^+), 352; Anal. calcd for $C_{21}H_{31}NO_7$: C, 61.61; H, 7.58; N, 3.42; found: C, 61.69; H, 7.62; N, 3.37.