Tetrahedron Letters 51 (2010) 6893–6896

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Tandem one-pot synthesis of α-(aminomethylene)-γ-butyrolactones via regioselective epoxide ring-opening with the Blaise reaction intermediate

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ARTICLE INFO

Article history:
Received 17 September 2010
Revised 19 October 2010
Accepted 22 October 2010
Available online 28 October 2010

Keywords:
Tandem reaction
Blaise reaction intermediate
Epoxide opening
Butyrolactone
Regioselectivity

ABSTRACT

A novel tandem one-pot method for the synthesis of α-aminomethylene-γ-butyrolactone derivatives has been developed through the regioselective epoxide opening reactions with the Blaise reaction intermediates, generated by the reaction of a Reformatsky reagent with nitriles. Formation of a modified Blaise reaction intermediate by the addition of a stoichiometric amount of *n*-BuLi followed by slow addition of epoxide is required for the good yield of γ-butyrolactones.

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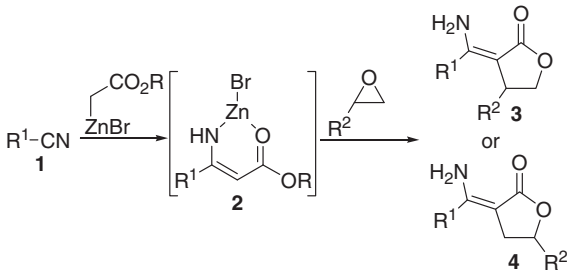
Tandem and cascade reactions have attracted significant attention because of their undeniable benefits such as atom economy and one-pot operation with maximization of molecular complexicity. Indeed, the device and implementation of tandem reactions are challenging facets and have become increasingly important in organic synthesis.[1] We have recently interested in the application of the Blaise reaction intermediate **2**,[2] generated by nucleophilic addition of a Reformatsky reagent to nitriles, for tandem bond formations, and demonstrated its nucleophilic nature: α-carbon and/or β-nitrogen act as nucleophilic sites allowing tandem synthesis of α-acylated,[3a,b] α-vinylated β-enaminoesters,[3c] and 2-pyridones.[3d] As the result of our continued research on the Blaise reaction intermediate, we report herein a novel tandem one-pot synthesis of β-substituted **3** or γ-substituted α-aminomethylene-γ-butyrolactones **4** via regioselective epoxide opening reaction with the Blaise reaction intermediate **2** (Scheme 1).

γ-Lactones are ubiquitous in many natural products and biologically active compounds, and also used as a versatile building block for the synthesis of a wide range of bioactive compounds.[4] Although a variety of synthetic routes have been developed,[5] nucleophilic epoxide ring-opening with enolates followed by intramolecular transesterification is the most general synthetic method for γ-butyrolactones.[6] However, in the literature, there are very limited precedents for one-pot synthesis of α-aminomethylene-γ-butyrolactones from nitriles: the recently developed Re-catalyzed cross-coupling of nitrile with lactones is the only general one-pot method for this class of compounds.[7] In this context, our tandem process not only discloses the distinctive reactivity profile of the Blaise reaction intermediate in the epoxide ring-opening reaction but also provides a new method to synthesize β-substituted **3** or γ-substituted α-aminomethylene-γ-butyrolactone derivatives **4** from nitriles in one-pot manner.

Initially, we anticipated that the Blaise reaction intermediate could act as a nucleophile in the epoxide ring-opening since it can be considered as a nitrogen isostere of the zinc enolate of the β-ketoesters.[8] In this scenario, we assumed that the zinc(II) complex **2** may act dual functions as a Lewis acid to activate the epoxide ring and as a nucleophile. We commenced our investigation with the Blaise reaction intermediate **2a** (R^1 = Ph, R = Et), formed



Scheme 1. Strategy for the tandem one-pot synthesis of γ-butyrolactones.

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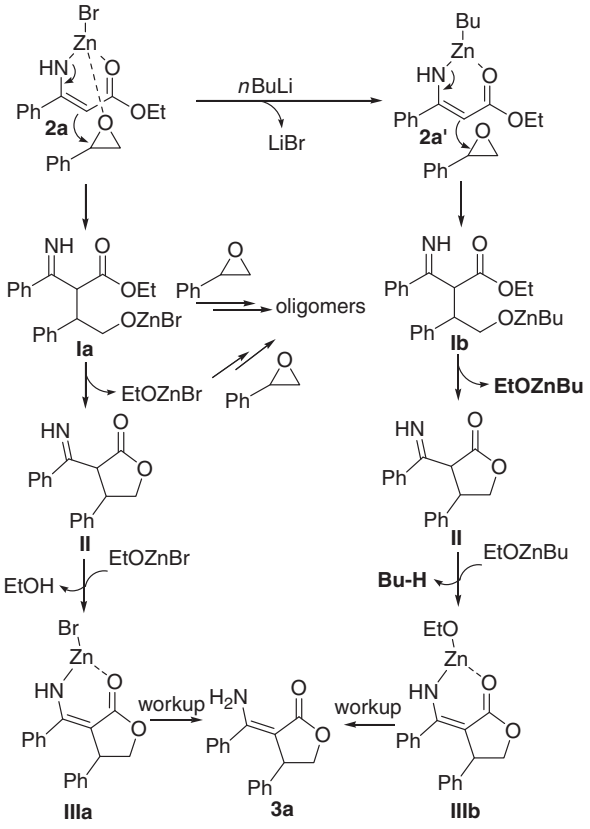
doi:10.1016/j.tetlet.2010.10.108

(>98% conversion by GC) by the reaction of benzonitrile (**1a**) with a Reformatsky reagent generated in situ from ethyl bromoacetate (1.5 equiv) and zinc (3.0 equiv) in THF. To this solution was added styrene oxide (1.2 equiv) at 0 °C, and the reaction continued for 24 h at room temperature to afford, after workup with satd NH_4Cl aqueous solution, the β-phenyl substituted α-aminomethylene-γ-butyrolactone **3a** in 43% yield with exclusive regioselectivity resulted from the epoxide ring-opening at the more substituted carbon (entry 1, Table 1).

To improve the moderate yield, we first varied the reaction temperature. Unfortunately, the yield was gradually dropped as the reaction temperature increased resulting **3a** in 38% at room temperature (entry 2, Table 1) and in 31% at THF reflux temperature (entry 3, Table 1). Addition of Lewis acidic $ZnBr_2$ or prolonged addition of epoxide did not improve the yield (entries 4 and 5, Table 1). Under these reaction conditions, all epoxide was consumed, but the Blaise reaction intermediate was always remained. This observation suggested that the epoxide may react with other nucleophiles such as **Ia** and EtOZnBr, which may be generated during the reactions. The lactonization reaction of the initially formed **Ia** may compete with epoxide ring-opening reaction affording oligomers. In addition, EtOZnBr, generated after lactonization of **Ia**, could also react with epoxide (Scheme 2). To solve this problem, we added an equivalent amount of *n*BuLi to generate the butylzincate **2a′** via ligand exchange with zinc bromide. With this zinc species, the EtOZnBu would be generated after lactonization, and then the proton exchange between **II** and EtOZnBu could produce the non-nucleophilic Bu–H and ethoxyzincate **IIIb**, which can be converted into product **3a** after workup with satd NH_4Cl aqueous solution (Scheme 2). Thus, 1.0 equiv of *n*BuLi was added to the Blaise reaction intermediate at 0 °C, and then styrene oxide was added at 35 °C. After 12 h, the product **3a** was obtained in a slightly increased yield of 50% (entry 6, Table 1). When the epoxide (3.0 M in THF) was added over 12 h, the yield increased further to 58% (entry 7, Table 1). Eventually, we found that slow addition of epoxide at 45 °C is critical for lactone ring formation, and thus, desired product **3a** could be obtained in 70% yield by addition of epoxide at 45 °C for 12 h (entry 8, Table 1).[8] However, addition of epoxide at THF reflux temperature decreased the yield slightly to 65% (entry 9, Table 1). Moreover, as we observed in our previous tandem

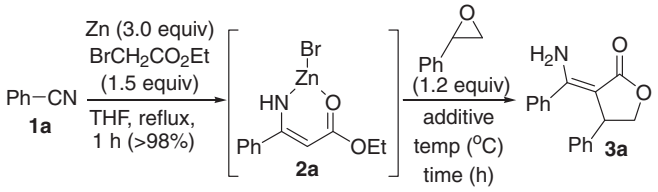


Scheme 2. Proposed mechanism for epoxide opening with the Blaise reaction intermediate **2a** and the ligand exchanged butylzincate **2a′**.

acylation reactions,[3a] the addition of other non-nucleophilic strong bases such as NaHMDS (entry 10, Table 1) or ^{t}BuLi (entry 11, Table 1) did not provide any beneficial effect on the Blaise reaction intermediate toward epoxide ring-opening.

Under the optimized reaction conditions[9] the generality of this tandem reaction has been investigated with aromatic and aliphatic nitriles to open the styrene oxide. As shown in Table 2, the Blaise

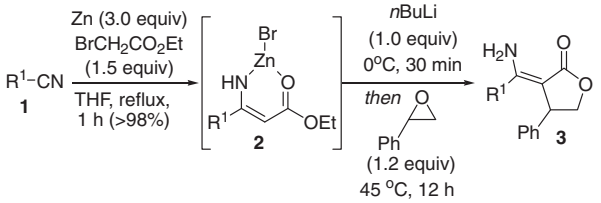
Table 1
Condition optimization for the tandem one-pot synthesis of β-phenyl substituted γ-butyrolactone **3a** via epoxide ring-opening with the Blaise reaction intermediate[a]

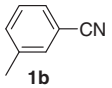
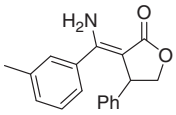
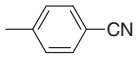
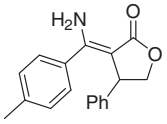
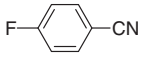
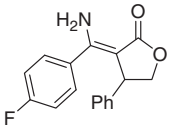
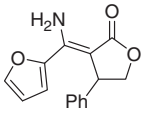
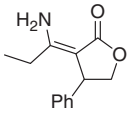
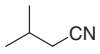
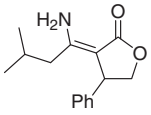
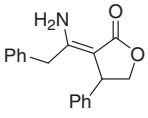


Entry	Additive	Temp (°C)	Addition time (h)	Reaction time (h)	Yield (%)[c]
1	—	0	—	24	43
2	—	rt	—	12	38
3	—	Reflux	—	12	31
4	$ZnBr_2$ (30 mol %)	0	—	12	40
5	—	35	12	12	37
6[b]	*n*BuLi (1.0 equiv)	35	—	3	50
7[b]	*n*BuLi (1.0 equiv)	35	12	12	58
8[b]	*n*BuLi (1.0 equiv)	45	12	12	70
9[b]	*n*BuLi (1.0 equiv)	Reflux	12	12	65
10[b]	NaHMDS (1.0 equiv)	45	12	12	37
11[b]	^{t}BuLi (1.0 equiv)	45	12	12	55

[a] Reaction carried out with 5.0 mmol scale of **1a** and zinc was pre-activated with 5 mol % of methanesulfonic acid in THF reflux.
[b] Additive was added at 0 °C.
[c] Isolated yield after column chromatography.

Table 2
Condition optimization for the tandem one-pot synthesis of β-phenyl substituted γ-butyrolactone **3** via styrene oxide ring-opening with the Blaise reaction intermediate[a]

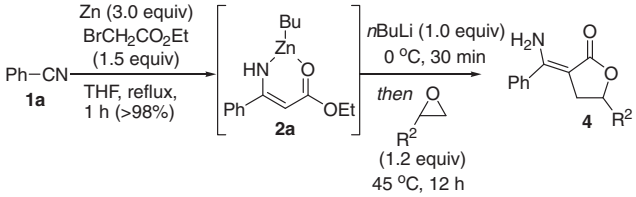


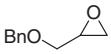
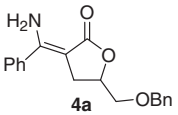
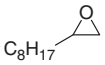
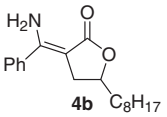
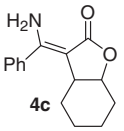
Entry	1	3	Yield[b] (%)
1	 **1b**		**3b** (72)
2	 **1c**		**3c** (72)
3	 **1d**		**3d** (61)
4	 **1e**		**3e** (51)
5	CH_3CH_2-CN **1f**		**3f** (68)
6	 **1g**		**3g**(42)
7	 **1h**		**3h**(57)

[a] Reaction carried out with 5.0 mmol scale of **1** and zinc was pre-activated with 5 mol % of methanesulfonic acid in THF reflux.
[b] Isolated yield after column chromatography.

reaction intermediates, formed from all aromatic and aliphatic nitriles with a Reformatsky reagent, reacted with styrene oxide at more substituted carbon to afford the corresponding β-substituted α-aminomethylene-γ-butyrolactones in moderate to good yields. The structures of **3** were unambiguously determined by ^1H and ^{13}C NMR analyses as well as X-ray analyses of **3a** and **3d**

Table 3
Condition optimization for the tandem one-pot synthesis of γ-substituted γ-butyrolactone **4** via epoxide ring-opening with the Blaise reaction intermediate **2a**[a]



Entry	Epoxide	4	Yield[b] (%)
1		 **4a**	**4a** (73)
2		 **4b**	**4b** (57)
3		 **4c**	**4c** (38)

[a] Reaction carried out with 5.0 mmol scale of **1a** and zinc was pre-activated with 5 mol % of methanesulfonic acid in THF reflux.
[b] Isolated yield after column chromatography.

(Fig. 1).[10] The electronic and steric properties of the substituent showed marginal effect on the yield (entries 1–3, Table 2). With aliphatic nitriles, the Blaise reaction intermediate formed from sterically less demanded propionitrile **1f** (entry 5, Table 2) showed higher yield than that obtained from sterically bulky isovaleronitrile **1g** (entry 6, Table 2).

We next investigate the aliphatic epoxides with the Blaise reaction intermediate **2a** (Table 3). In contrast to the styrene oxide, the alkylsubstituted ethylene oxides are opened at sterically less demanded terminal carbon to afford the γ-substituted γ-butyrolactones as determined by X-ray analysis of **4a** (Fig. 1).[11] These results imply that the regioselectivity of epoxide ring-opening with the Blaise reaction intermediate is dependent on the nature of epoxides, that is, in styrene oxide, the regioselectivity of the nucleophilic attack of the Blaise reaction intermediate was determined by their electronic property, whereas steric factor is more dominant in alkylsubstituted ethylene oxides. Even though the yield was low, the less reactive cyclohexene oxide can also be opened with the Blaise reaction intermediate to afford the cyclic lactone **4c**.

In summary, we have developed a novel tandem one-pot method for the synthesis of β-substituted or γ-substituted α-(aminomethylene)-γ-butyrolactones through the regioselective epoxide

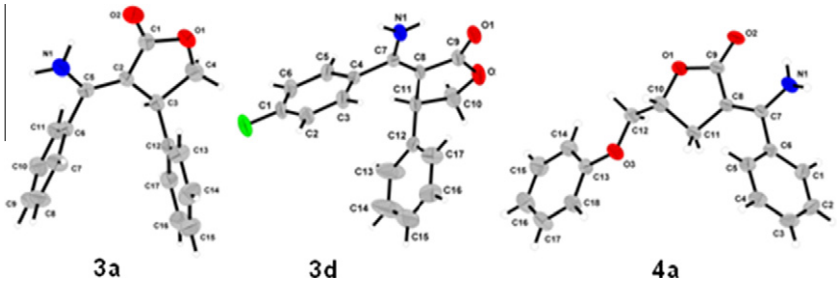


Figure 1. X-ray structures of **3a**, **3d**, and **4a**.

ring-opening reaction with the Blaise reaction intermediate, where the regioselectivity of epoxide ring-opening was largely determined by the steric and electronic nature of epoxide. A modification of the addition of a stoichiometric amount of *n*-BuLi to the Blaise reaction intermediate increased its reactivity toward the epoxide opening reaction and lactonization to provide α-(aminomethylene)-γ-lactones efficiently. Further applications of the Blaise reaction intermediate to other conceivable reactions are underway and will be reported in due course.

Acknowledgments

This work was supported by the Korea Research Foundation (KRF-20090070898 and KRF-20090063004), the Seoul R&D fellowship for Y. O. Ko, and RP-supporting from Ewha Womans University for Y. S. Chun.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.108.

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8. When the reaction mixture was workedup with 3 N aqueous HCl solution, the α-benzoylated β-phenyl-γ-butyrolactone was isolated in 68% yield. It has been previously reported that reaction of ethyl acetoacetate with styrene oxide in the presence of sodium ethoxide afforded a mixture of β-phenyl- and γ-phenyl substituted α-acetyl-γ-butyrolactones in 45% and 55% yield, respectively, see: Reitz, D. B. *J. Org. Chem.* **1979**, *44*, 4707.
9. Typical experimental procedure: to a stirred suspension of zinc dust (Aldrich, 10 μm, 1.0 g, 15.3 mmol) was added 6 mol % of methanesulfonic acid in anhydrous THF (2.5 mL). After 10 min reflux, benzonitrile **1a** (0.8 mL, 7.6 mmol) was added. While maintaining reflux temperature, ethyl bromoacetate (1.26 mL, 11.4 mmol) was added over 1 h by using a syringe pump, and the reaction mixture was refluxed for 1 h. The reaction mixture was cooled to 0 °C, and an equivalent amount of *n*-BuLi (4.75 mL of 1.6 M in hexane solution, 7.6 mmol) was added at 0 °C. The 3.0 M solution of styrene oxide (1.05 mL, 7.6 mmol) in THF was added slowly for 12 h at 45 °C. The reaction was quenched with aqueous satd NH_4Cl solution at room temperature, and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated. The residue was purified by silica chromatography to afford **3a** (1.41 g, 70%).
10. Crystal data for **3a** (CIF deposition number: CCDC793437): $C_{17}H_{15}NO_2$, momoclinic, $P2_1/c$, $a = 6.0057(9)$ Å, $b = 10.3248(15)$ Å, $c = 22.742(3)$ Å, $V = 1407.8(4)$ Å^3, $Z = 4$, $D_c = 1.252$ g/m^3, $F(0\,0\,0) = 560$,7721 independent collections with $I/2\sigma(I)$ ($R1 = 0.0366$, w$R2 = 0.0531$), *GOF* (F^2) = 0.600 data for crystallographic analysis were measured on a Bruker SMART APX diffractometer using graphite-monochromate Mo KR (λ 0.71073 Å) and ω-2 scans in the range of θ, $1.79 < \theta < 26.00$. Crystal data for **3d** (CIF deposition number: CCDC 793438): $C_{17}H_{14}FNO_2$, momoclinic, $P2_1/c$, $a = 13.707(3)$ Å, $b = 9.6840(19)$ Å, $c = 11.622(2)$ Å, $V = 1437.9(5)$ Å^3, $Z = 4$, $D_c = 1.309$ g/m^3, $F(0\,0\,0) = 592$,7634 independent collections with $I/2\sigma(I)$ ($R1 = 0.0560$, w$R2 = 0.1453$), *GOF* (F^2) = 0.945 data for crystallographic analysis were measured on a Bruker SMART APX diffractometer using graphite-monochromate Mo KR (λ 0.71073 Å) and ω-2 scans in the range of θ, $1.59 < \theta < 26.00$. Structure was solved and refined by using the SHEL V6.12.
11. Crystal data for **4a** (CIF deposition number: CCDC 793436): $C_{18}H_{17}NO_3$, momoclinic, $P2_1/c$, $a = 12.320(2)$ Å, $b = 10.1168(16)$ Å, $c = 12.1529(19)$ Å, $V = 1512.8(4)$ Å^3, $Z = 4$, $D_c = 1.297$ g/m^3, $F(0\,0\,0) = 624$,7619 independent collections with $I/2\sigma(I)$ ($R1 = 0.0566$, w$R2 = 0.1605$), *GOF* (F^2) = 1.062 data for crystallographic analysis were measured on a Bruker SMART APX diffractometer using graphite-monochromate Mo KR (λ 0.71073 Å) and ω-2 scans in the range of θ, $2.61 < \theta < 26.00$. Structure was solved and refined by using the SHEL V6.12.