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Efficient Medium Ring Size Bromolactonization Using a Sulfur-Based Zwitterionic Organocatalyst

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Supporting Information

ABSTRACT: Catalytic bromolactonization of long-chain olefinic acids resulting in the efficient synthesis of medium-sized lactones is reported using a zwitterionic catalyst and stoichiometric *N*-bromosuccinimide halogen source. The reaction was found to be more efficient at 0 °C than at room temperature, which could be attributed to the temperature dependence of the zwitterionic catalyst.

Medium ring size lactones, seven- to nine-membered lactones, for example, are the fundamental units of many natural products.[1] However, the synthesis of these medium-sized lactones remains a challenging task, in which both enthalpic and entropic factors impede the cyclization of a linear substrate to form a medium-sized ring.[2] A substrate with a long carbon backbone has a high degree of conformational flexibility, and consequently negative entropic change results during the ring closing reaction. The enthalpic factor arises from several steric factors, of which transannular strain is the most highly prevalent in medium-ring formation.[3] Illuminati and co-workers demonstrated that such cyclizations are difficult to achieve as the rate of cyclization of ω-bromoalkanoic acids to form seven-membered lactones were found to be more than 10^4 times slower, and eight- and nine-membered lactones 10^6 times slower, relative to the formation of five-membered lactones.[4]

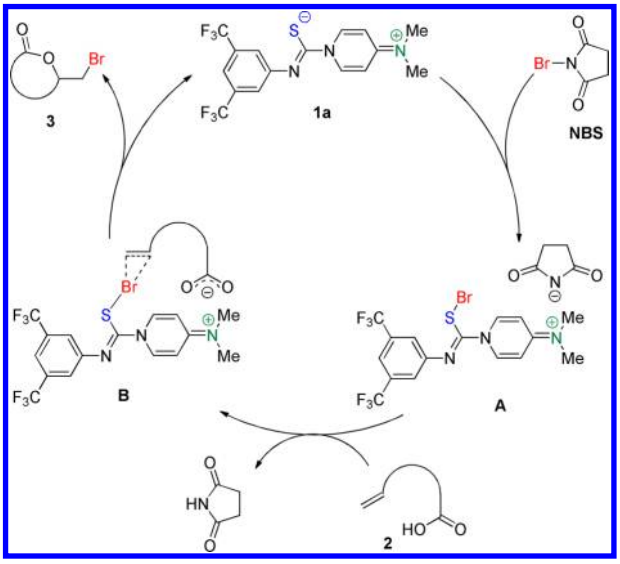
Several ring closure reactions of bifunctional aliphatic molecules, including olefin metathesis[5] and lactonization using hydroxyl carboxylic acid substrates,[6] have been documented.[7] High-dilution and/or slow addition techniques are usually employed to avoid undesired intermolecular reaction between the substrates. To overcome the thermodynamic barriers to the cyclization, high temperature or metal-based catalysts is sometimes used.[8] Hence, a mild and efficient method to synthesize such medium rings would be highly desirable and is envisaged to have great utility in organic synthesis.

Halolactonization of olefinic substrates is a powerful method in the formation of lactones. The resultant halogens on the lactones can easily be manipulated, which provide flexible handles for further functionalization. Significant efforts have been devoted to research on various methods to synthesize small halolactones, i.e., five- and six-membered lactones.[9] In a sharp contrast, the application of halolactonization to medium-ring lactone synthesis is very uncommon since a suitable reaction protocol is elusive. A representative example was reported by Rousseau and co-workers, in which a highly reactive bis(*sym*-collidine)iodine(I) hexafluorophosphate was used as the stoichiometric halogen source in the medium-sized iodolactone formation.[10] Herein we describe a facile and efficient approach toward the construction of medium-sized lactone using a zwitterion as the catalyst (5 mol %) and *N*-bromosuccinimide (NBS) as the stoichiometric halogen source.

Zwitterion **1a** was used in our study, and **1a** can easily be synthesized using Ishihara's approach by a one-step reaction between 3,5-(bistrifluoromethyl)phenyl isothiocyanate and *N*,*N*-dimethylaminopyridine (DMAP). The structure of **1a** was unambiguously confirmed by an X-ray crystallographic study.[11] Surprisingly, this interesting class of catalyst has only been applied in the trans-esterification reactions.[12] In fact, zwitterionic catalysts are useful in organic synthesis. For instance, Ooi et al. recently developed several elegant zwitterionic protocols which were found to be useful in some important reactions.[13]

In electrophilic halolactonization, a widely accepted mechanism is that an electrophilic halogen is first transferred from a halogen source to an olefin to form a halonium ion, followed by an intramolecular attack by a carboxylate group.[9] Zwitterion **1a** contains an anionic sulfur and a cationic nitrogen centers (Scheme 1 and Figure S1).[12,14] We rationalize that the basic

Scheme 1. Strategy of Zwitterion Catalyzed Bromolactonization



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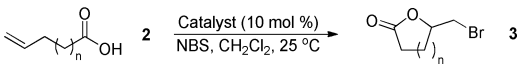
sulfur in zwitterion **1a** could react with NBS to give intermediate **A**; this interaction could effect the dissociation of NBS and could offer a highly electrophilic Br source (Scheme 1).[15] Ion exchange between the succinimide anion and the carboxylic acid could next give the corresponding ammonium carboxylate, and the sulfur activated bromide could react with the olefin to yield intermediate **B**. The proximity of the carboxylate anion and the bromonium ion ring could then facilitate the cyclization to furnish the lactone, and zwitterion **1a** could be regenerated.

To test this hypothesis, we examined the bromolactonization of 4-pentenoic acid (**2a**) and NBS in CH_2Cl_2 at 25 °C (Table 1). In the absence of catalyst, the reaction was sluggish and

Table 1. Bromolactonization of 2 Using Different Catalysts[a]



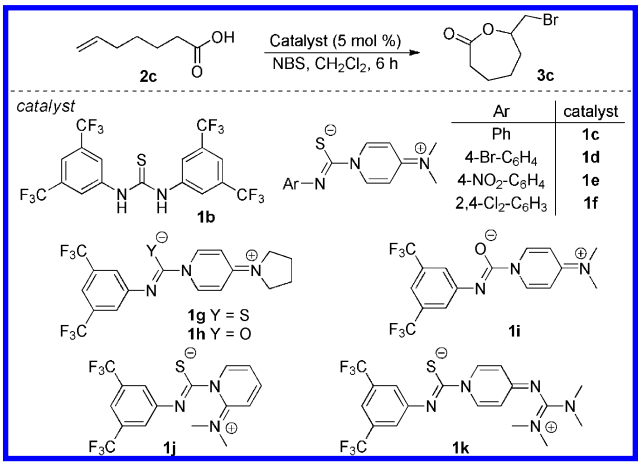
entry	catalyst	substrate, *n*	time (h)	isolated yield (%)
1	none	**2a**, 1	54	99
2	**1a**	**2a**, 1	0.75	92
3	DMAP	**2a**, 1	5	69
4	DABCO	**2a**, 1	3	92
5	DMF	**2a**, 1	18	49
6	DBU	**2a**, 1	7	94
7	HMPA	**2a**, 1	3.5	92
8	**1a**	**2b**, 2	6	89

[a]Reactions were carried out with olefinic acid **2** (0.25 mmol), catalyst (0.025 mmol), NBS (0.5 mmol) in CH_2Cl_2 (5.0 mL). DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = diazabicyclo[5.4.0]undec-7-ene, HMPA = hexamethylphosphamide.

completed in 54 h (Table 1, entry 1). In the presence of 10 mol % of **1a**, the reaction rate was increased dramatically, and the lactonization was complete in 45 min (Table 1, entry 2). A comparison of the effect of some common Lewis base catalysts is listed in Table 1, showing the superiority of the catalytic activity of zwitterion **1a**.

Having demonstrated the catalytic ability of **1a**, we further examined the lactonization of larger ring systems. Bromolactonization of 5-hexenoic acid (**2b**) proceeded smoothly, producing lactone **3b** in 89% (Table 1, entry 8). The formation of seven-membered lactone was less effective, in which 25% yield of **3c** was obtained after 6 h (Table 2, entry 1). Attempts to vary the reaction temperature, interestingly, led us to identify that the reaction proceeded smoother at lower temperature; at 0 °C, 54% of lactone **3c** was isolated in 6 h, with the use of 5 mol % of **1a** (Table 2, entry 2). In comparison, a lower yield was obtained at 0 °C than at 25 °C when using DMAP as the catalyst (Table 2, entries 3 and 4). Other catalysts including *N*,*N*-[3,5-bis(trifluoromethyl)phenyl]thiourea (catalyst **1b**), Lewis acidic (Table 2, entry 10) and basic (Table 2, entries 11−15) catalysts displayed little or no reactivity. Catalysts with different *N*-Ar substituents (i.e., catalyst **1c**−**f**) and amino group (i.e., catalyst **1g**) returned with lower conversions (Table 2, entries 16−20). When the sulfur atom was replaced with oxygen (i.e., catalysts **1h** and **1i**), the product yield was greatly diminished and demonstrated the importance of the sulfur as the catalytic center (Table 2, entries 21 and 22). Interestingly, catalysts **1j** and **1k** gave a lower yield than **1a**, suggesting that the space between the cation and the anion may be critical (Table 2, entries 23 and 24). In the investigation of different

Table 2. Bromolactonization of 2c[a]



entry	catalyst	temp (°C)	yield (%)
1	**1a**	25	25
2	***1a***	***0***	***54***
3	DMAP	25	23
4	DMAP	0	19
5	**1a**	−8	36
6	**1a**	−15	9
7	**1a**	−52	trace
8	**1a**	−78	trace
9	**1b**	0	trace
10	$SnCl_4$	0	trace
11	DBU	0	15
12	DABCO	0	10
13	Ph_3P	0	trace
14	Ph_3PS	0	trace
15	$(Me_2N)_2CS$	0	trace
16	**1c**	0	10
17	**1d**	0	33
18	**1e**	0	33
19	**1f**	0	46
20	**1g**	0	30
21	**1h**	0	12
22	**1i**	0	17
23	**1j**	0	trace
24	**1k**	0	9
25[b]	**1a**	0	trace
26[c]	**1a**	0	27

[a]Reactions were carried out with 6-heptenoic acid (**2c**) (0.25 mmol), catalyst **1** (0.0125 mmol), NBS (0.5 mmol) in CH_2Cl_2 (5.0 mL). The yields were isolated yields. [b]*N*-chlorosuccinimide was used as the halogen source. [c]*N*-iodosuccinimide was used as the halogen source.

halogen sources, it was found that both *N*-chlorosuccinimide and *N*-iodosuccinimide did not perform better than NBS (Table 2, entries 25 and 26).

The scope and utility of this reaction are indicated by the 12 examples listed in Table 3. Excellent regioselectivities were observed for the formation of seven-, eight-, and nine-membered lactones which the exocyclized products were obtained exclusively.[16] In comparison, lower yields for the corresponding iodolactones of **3j**, **3k**, and **3o** were reported using bis(*sym*-collidine)iodine(I) hexafluorophosphate as the stoichiometric halogenating reagent.[10b] Notably, in the case of formation of **3i** and **3m**, parallel experiments were performed using DMAP (5 mol %) as the catalyst under the same

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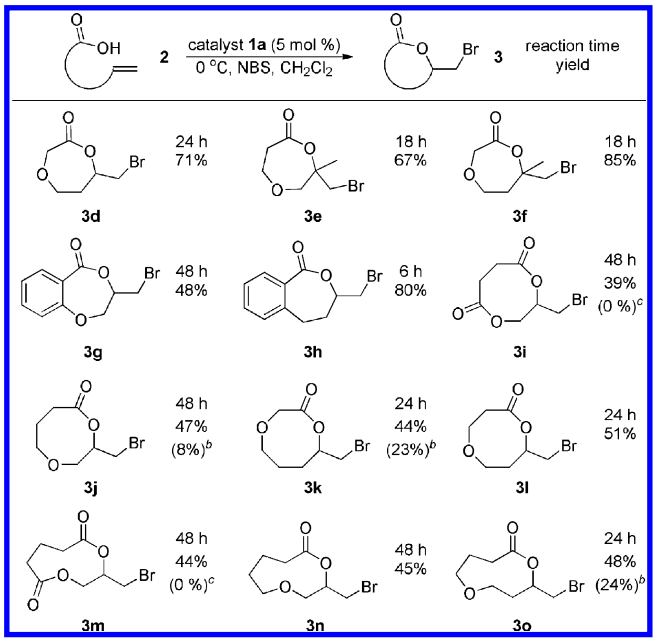
Table 3. Bromolactonization of 2[a]



[a]Reactions were carried out with olefinic acid **2** (0.25 mmol), catalyst **1a** (0.0125 mmol), NBS (0.5 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C. The yields were isolated yields. [b]The parentheses indicates the yield of the corresponding iodolactone when using bis(*sym*-collidine)iodine(I) hexafluorophosphate as the stoichiometric halogen source. For detail, see ref 10b. [c]The parentheses indicate the yield when using DMAP (5 mol %) as the catalyst.

conditions, and no reaction was observed. In all cases, slow addition and high dilution were unnecessary to avoid the dimerization/oligomerization process.[10a,17]

During our investigation, several interesting phenomena were observed which allow us to get a better understanding on this reaction. In the study on the temperature effect of the zwitterion **1a** catalyzed lactonization, we noticed that the catalyst solution was colorless at 25 °C (Figure 1). However, the solution turned light yellow at 0 °C and changed to bright yellow at even lower temperatures, which resembled the color of the pure crystalline zwitterion **1a**. This color change was reversible. We speculated that the color change could be attributed to the equilibrium in favor of zwitterion **1a** over the individual starting materials (i.e., DMAP and 3,5-bis-(trifluoromethyl)isothiocyanate) in solution phase at low temperature.

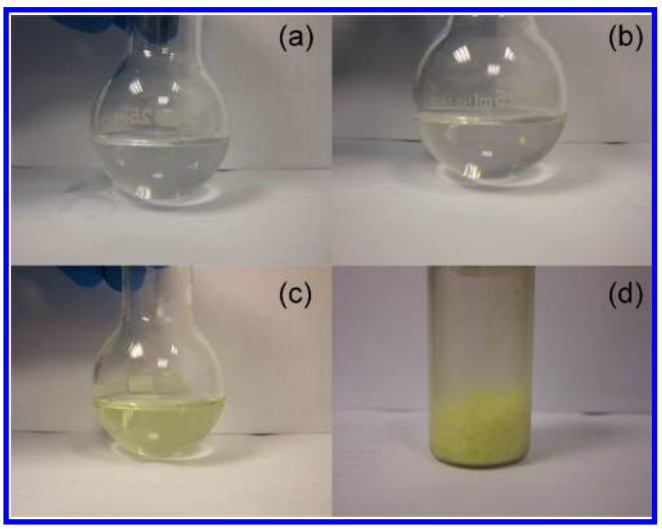


Figure 1. Zwitterion **1a** color: (a) Pure CH_2Cl_2 at 25 °C, and **1a** in CH_2Cl_2 (0.05 M) at (b) 25 °C and (c) −40 °C. (d) Pure crystalline **1a**.

Low-temperature ^{1}H NMR experiments were performed to get further insight of this phenomenon. The methyl signals of **1a** (3.25 ppm) and DMAP (3.00 ppm) were taken as reference points in the comparison of the zwitterion **1a**:DMAP ratio (Figure S2).[11] At 298 K, the **1a**:DMAP ratio was found to be 1:17. As the temperature decreased, the **1a**/DMAP ratio increased, and the ratio (11:1) became steady at below 233 K (Figure 2). This could provide an explanation that a better conversion was achieved at 0 °C than at 25 °C.

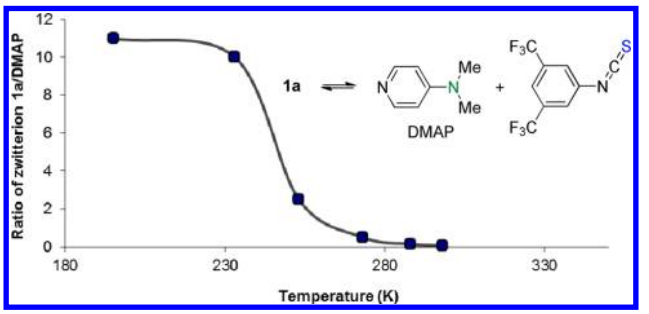


Figure 2. Relationship between the **1a**:DMAP ratio and the temperature.

Next, we examined the complex between NBS and zwitterion **1a**. A 1:1 mixture of NBS and **1a** gave a bright-yellow solution at room temperature. The ^{1}H NMR of such a mixture indicated that there were two species (ca. 2.5:1). A small amount of free catalyst **1a** was observed, but no free DMAP was detected (Figure S3).[11] Since the negative charge in **1a** can delocalize between S and N atoms,[18] we suspect that the two species might be the S−Br and N−Br complexes (i.e., Figure 3, **A** and **A′**). Although zwitterion **1a** and DMAP exist in equilibrium in the solution phase and could be active catalysts, as indicated in Table 1, NBS−**1a** complexes appear to be the dominant active species, since the NBS−DMAP complex was not observed in the NBS−**1a** ^{1}H NMR study (Figure S4).[11]

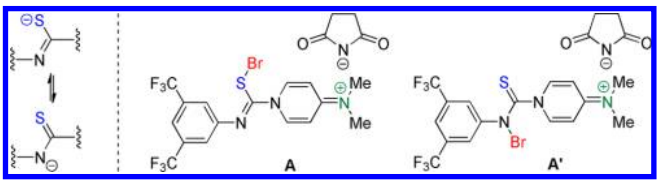


Figure 3. **1a**−NBS Complexes.

In summary, we have developed the first organocatalytic halolactonization of unsaturated carboxylic acids using zwitterion **1a**, resulting in the formation of medium-sized lactones. The catalyst can easily be synthesized by a one-step coupling between DMAP and isothiocyanate. NBS was used as the stoichiometric halogen source, which is inexpensive and readily available. The lactonization was found to be more efficient at lower temperature, potentially due to the more favorable catalyst formation. Further investigations on other applications and the mechanistic picture are underway.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental detail, CIF file of the X-ray structure, and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) We have also examined the formation of larger ring-sized lactones. Good yields were obtained, but the exo/endo selectivity dropped (see Scheme S1).

(17) Analysis on the crude product from Table 2, entry 2 using TLC, ^{1}H NMR, and LCMS showed that there was no significant signal corresponding to oligomeric product. However, starting material was consumed, and appreciable amounts of side products (by TLC and ^{1}H NMR, an inseparable mixture) were detected when using other catalysts (e.g., DMAP and DABCO); LCMS analysis on the side products showed several mass signals corresponding to oligomeric products.

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