



Molecular sieves as an efficient and recyclable catalyst for bromolactonization and bromoacetoxylation reactions

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ABSTRACT

Bromolactonization of unsaturated acids and bromoacetoxylation of olefins proceeded smoothly in the presence of molecular sieves and *N*-bromosuccinimide. The molecular sieves can be recycled and reused, and the halogen carrier can be recovered effectively.

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Electrophilic bromination of alkenes is a fundamental transformation in organic synthesis. The reactions are typically conducted in aqueous base using bromine or *N*-bromosuccinimide (NBS) as the halogen source.¹ An important research direction is the development of a solid base or acid as a green and recyclable catalyst. Some methods such as SiO₂/NBS,² Ti₂CO₃/Br₂³ and Amberlyst/NBS⁴ have been reported. However, recent studies have shown that the resource demands and amount of waste produced by many new halogenation methods are significantly higher than the standard process, especially if recycling of the halogen-carrying agent (e.g., succinimide) is not efficient.⁵ Herein we describe a resource efficient process for bromolactonization and bromoacetoxylation using molecular sieves (MS) and NBS.

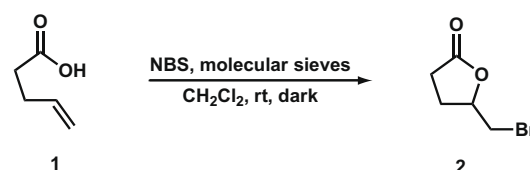
Molecular sieves are commonly used to absorb water and other small molecules.⁶ To our delight, we found that molecular sieves were able to catalyze bromolactonization and bromoacetoxylation reactions. Initially, the bromolactonization of 4-pentenoic acid (**1**) with NBS was carried out at room temperature. Without any catalyst, the reaction was complete in 54 h (Table 1, entry 1). In the presence of 3 Å molecular sieves (400 mg per mmol), the bromolactonization reaction proceeded to completion in just 5 min (Table 1, entry 2).⁷ Upon further examination, we were able to reduce the catalyst loading to 20 mg per mmol of **1**, producing lactone **2** in 98% yield in 4.5 h (Table 1, entry 7).⁸ It is important to note that the lactonization still proceeded smoothly on 1.0 g scale (Table 1, entry 10).⁹ In addition, in the absence of solvent the reaction was complete in 3 h in 92% yield.¹⁰ Among the molecular sieves examined (3 Å, 4 Å, 5 Å, and 13 X), 3 Å MS gave the best results (Table 1, entries 12–14).

The work-up procedure was extremely simple, involving filtration of the MS, precipitation of the succinimide, and removal of the solvent by distillation. The isolated product and the recycled halogen carrier were extremely pure (>99% purity by ¹H NMR).

Attempts to catalyze the same reaction with recycled molecular sieves were successful without significant loss of reactivity (Table 1, entries 8 and 9).

In addition to 4-pentenoic acid (**1**), we also examined the lactonization of several unsaturated acids and good yields of the expected products were obtained (Table 2). An *exo*-mode of cyclization was favored under kinetic conditions, in which the *cis*

Table 1
Bromolactonization of 4-pentenoic acid (**1**) catalyzed by various molecular sieves



Entry	Molecular sieves	Loading (mg/mmol)	Time	Yield ^a (%)
1	None	0	54 h	99
2	3 Å	400	5 min	99
3	3 Å	300	10 min	99
4	3 Å	200	20 min	98
5	3 Å	100	30 min	98
6	3 Å	40	75 min	99
7	3 Å	20	4.5 h	98
8 ^b	3 Å	20	4.5 h	97
9 ^c	3 Å	20	4.5 h	92
10 ^d	3 Å	20	9 h	93
11 ^e	3 Å	20	3	92
12	4 Å	20	10 h	97
13	5 Å	20	23 h	90
14	13 X	20	7.5 h	93

^a Isolated yields.

^b Reaction using first time recycled molecular sieves.

^c Reaction using second time recycled molecular sieves.

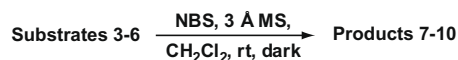
^d Reaction conducted using 1.0 g (10 mmol) of the substrate.

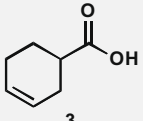
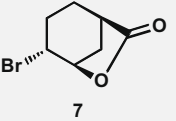
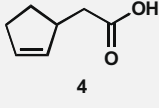
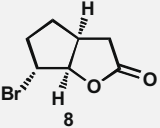
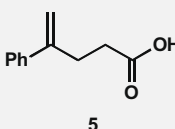
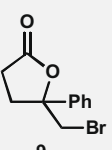
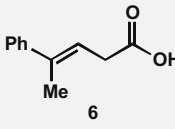
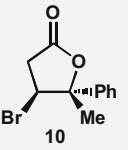
^e Reaction conducted without using solvent.

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Table 2
Bromolactonization of unsaturated acids **3–6**



Entry ^a	Substrate	Product	Cat. loading (mg/mmol)	Time (h)	Yield ^b (%)
1			20	7	94
2			100	9	83
3			20	9	93
4			20	8	91

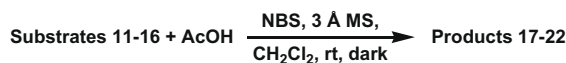
^a Reaction conditions: substrate (0.5 mmol), NBS (89 mg, 0.5 mmol), 3 Å MS (10 mg), CH₂Cl₂ (2 mL, 0.25 M).

^b Isolated yield.

stereochemistry at the ring junction of the bridged (Table 2, entry 1) and fused (Table 2, entry 2) lactones was preserved.¹¹ The stereocontrol in entry 4 (Table 2) could be attributed to the five-membered ring transition state in which the less bulky methyl group remained at the pseudo-axial position.¹²

Examination of intermolecular bromoacetoxylation reactions of various olefins confirmed the effectiveness of this protocol (Table 3).¹³ In entries 3 and 4, Markovnikov-type addition was observed. In general, the intermolecular bromoacetoxylation required higher MS loading in order to achieve a reasonable reaction rate.

Table 3
Bromoacetoxylation of olefins **11–16**



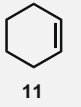
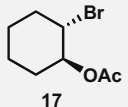
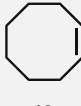
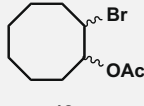

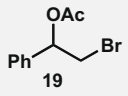
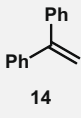
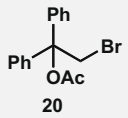
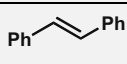
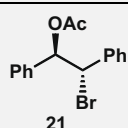

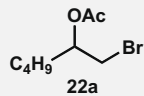
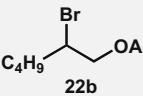
Entry ^a	Substrate	Product	Cat. loading (mg/mmol)	Time (h)	Yield ^b (%)
1			200	2	96
2 ^c			200	16	99
3 ^d			400	12	90
4 ^d			400	12	80

Table 3 (continued)

Entry ^a	Substrate	Product	Cat. loading (mg/mmol)	Time (h)	Yield ^b (%)
5			400	24	90
6		  (1 : 1)	400	12	67

^a Reaction conditions: substrate (1.0 mmol), NBS (178 mg, 1.0 mmol), AcOH (57 μ L, 1.0 mmol), CH₂Cl₂ (4 mL, 0.25 M).

^b Isolated yield.

^c cis:trans ratio was 2:1.

^d 4 equiv of AcOH were used.

Towards a mechanistic understanding of the reaction, we speculate the origin of the catalytic ability is due to the mild basicity of the molecular sieves. A simple basicity test showed approximately pH 9–10 for all the molecular sieves.¹⁴ We rationalize that the MS deprotonate the carboxylic acid to provide a nucleophilic carboxylate, which facilitates the lactonization and bromoacetoxylation. Nevertheless, base-sensitive esters and lactones tolerate the reaction conditions. In addition, β -bromolactone **10**, which has been known to readily undergo dehydrobromination under mildly basic conditions, was isolated in high yield.¹³

In summary, we have developed an efficient, column- and extraction-free bromolactonization of unsaturated carboxylic acids using NBS and 3 Å MS. The protocol can also be applied to the intermolecular bromoacetoxylation of olefinic substrates. The catalyst and the halogen carrying agent can be recycled effectively thereby demonstrating a resource efficient halogenation process. The application of this procedure to other reactions is under investigation.¹⁵

Acknowledgment

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- The molecular sieves were purchased from Aldrich and used as received without further treatment. Molecular sieves from other companies including Alfa and Acros worked equally well.
- Representative procedure for the bromolactonization: to a solution of 4-pentenoic acid (**1**) (102 μ L, 1.0 mmol) and 3 Å molecular sieves (20 mg) in CH₂Cl₂ (4 mL) was added *N*-bromosuccinimide (178 mg, 1.0 mmol) at room temperature. The resulting suspension was stirred vigorously for 4.5 h and filtered. The residue was washed with CH₂Cl₂ to recover the molecular sieves. The combined filtrate was concentrated under reduced pressure. The white solid paste obtained was diluted with *n*-hexanes (10 mL), filtered, and concentrated under reduced pressure to give lactone **2** (178 mg, 99%). The residue was dried to yield succinimide (121 mg, 99%).
- The longer reaction time was due to the unoptimized rate of stirring the suspension.
- A shaker was used instead of a magnetic stirrer as the reaction suspension was sticky.
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- All the products were characterized and the physical data were in full accordance with literature values.
- pH values were measured by stirring the suspension of molecular sieves in water for 10 min before testing using pH paper.
- Preliminary results indicated that 5 Å MS catalyzed the bromoetherification of 4-penten-1-ol in 66% yield.