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Concise bromodecarboxylation of cinnamic acids to β-bromostyrenes

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ABSTRACT

A convenient salt-free approach to the halodecarboxylation of cinnamic acid analogs to β-bromostyrene was reported. This conversion was conducted at 0 °C in CH_2Cl_2 with only 10% of acetic acid. This protocol can be used for cinnamic acids with a variety of substituents, including β-methyl cinnamic acid (**1d**) in 60–81% yield, but not for hydroxyl- and *p*-methyl-cinnamic acids. Meanwhile, pyridine hydrobromide perbromide was used as bromide source to convert **1a**–**2a** in 59% yield.

Vinyl bromide is a useful synthon in organic synthesis, especially in palladium and copper chemistry.[1] It has been used to synthesize stilbenoids,[2] pyridines,[3] and *N*-alkenyloxazolidin-2-one.[4] Moreover, vinyl bromide is a key agent for introducing styrene moieties in natural product synthesis.[5]

Halodecarboxylation of the corresponding carboxylic acid is widely used to obtain bromides. Among existing methods, the Hunsdiecker reaction is a popular approach; however, this reaction requires a heavy metal salt and high reaction temperature, which restricts its application. Besides, the classical Hunsdiecker reaction is very inefficient for cinnamic acid analogs, for example, the bromodecarboxylation of cinnamic acids under classical conditions gives the desired product in less than 15% yield.[6] It is therefore infeasible to synthesize vinyl bromide via this approach. Thereafter, several attempts to improve the Hunsdiecker reaction to convert cinnamic acids to corresponding bromide was made with various reagents and conditions, however, salt or certain equipments such as microwave reactor is still needed.[7]

The straightforward bromination of a cinnamate salt, which was first reported in 1921,[8] gives a bromohydrin as the major product. In addition to bromohydrin, trace amounts of bromostyrene are produced; this product is believed to derive from the elimination of bromohydrin in the evaporation process rather than from the bromination reaction itself. In this reaction, reaction yield is sensitive to water volume. Therefore, the starting material must be in the form of a salt for better water solubility. When carbon tetrachloride or chloroform was used as the reaction solvent, halogenation was found to occur on the olefin of cinnamic acid.[9] In comparison, when the cinnamate ester was exposed to bromine or chlorine in acetic acid, dihalogenation and acetoxylhalogenation of the olefin were observed.[10] In other work in this area, Cabaliero and Johnson found that the chlorination of *trans*-cinnamic acid in acetic acid in the presence of lithium acetate gave α,α,β-trichlorostyrene and α,α-dichloro-β-acetoxyl-styrene, and suggested that these products were generated by further halogenations of β-chlorostyrene.[11] In these experiments, β-chlorostyrene was not isolated from the reaction mixture. Additionally, Cabaliero and Johnson found that the use of a salt as the reactant is crucial for the conversion of carboxylic acids to the corresponding chlorides.

The synthesis of bromostyrene from the corresponding cinnamate was reported by Kingsbury and Max.[12] When substituted cinnamates were treated with bromine in methanol or water, bromodecarboxylation or β-lactonization occurred. Although β-bromostyrene was one of the products identified, the isolated mixture contained β-bromostyrene and two further brominated compounds, tribromoethylbenzene and bromohydrine. Although the bromodecarboxylated product was identified in this experiment, the cinnamate ion is still necessary in this reaction. If the free acid is used instead of the salt under the same conditions, bromination or bromohydrination of the olefin occurs without any decarboxylation. Recently, oxidative halodecarboxylation of cinnamic acid analogs was achieved with NBS as a brominating agent.[13] In the presence of either iodosylbenzene or iodosylbenzene diacetate,

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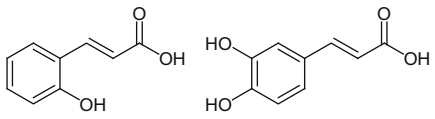


6 7

Figure 1. Two compounds subjected to bromodecarboxylation.

the yield of halostyrene is 32–89%. Cinnamic acid can also be converted to bromostyrene by applying diphosphorous tetraiodide in combination with tetraethylammonium bromide in CS_2.[14]

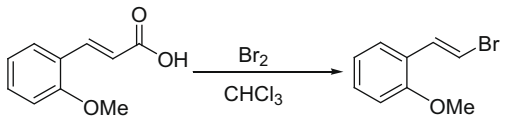
In addition, β-halostyrene can be prepared from the corresponding carboxylic acid via carboxyl-halo-elimination of cinnamic acid derivatives. For example, treatment of dibromophenylpropionic acid with triethylamine in DMF at room temperature affords β-bromostyrene. However, only the *cis*-olefin is obtained and two steps are considered necessary.[15] Although there are practical approaches for converting cinnamic acids to bromostyrene, the methods developed to date have drawbacks including the requirement for multiple steps, complex or dangerous reagents, and tedious work-up procedures. Thus, a convenient halodecarboxylation method is still needed (Fig. 1)

Herein, we report a convenient approach to the halodecarboxylation of cinnamic acid analogs that does not require any salt. Firstly, 2-methoxycinnamic acid (**1a**) was treated with bromine in chloroform at 0 °C and β-bromo-2-methoxystyrene (**2a**) was isolated in 23% yield. The low solubility of compound **1a** in $CHCl_3$ may be the reason for the low yield. To improve the solubility of **1a**, acetic acid was added to the reaction media and CH_2Cl_2 was used instead of $CHCl_3$. The results are summarized in Table 1 and the reaction proceeds in 10% v/v acetic acid in CH_2Cl_2 yielding compound **2a** in 67%. To the best of our knowledge, this is the most convenient process for this kind of transformation (Scheme 1).

Encouraged by this result, we subjected various cinnamic acid analogs, including fluorinated, aminated, hydroxylated, and methoxylated analogs, to the reaction conditions established above; the results are summarized in Table 2. The reaction afforded β-bromostyrenes in moderate to good yield, except the *p*-methylated and hydroxylated ones. In the case of the β-methylated analog **1d**, the reaction gave the dibromide **2d** in 60% yield and did not give any of the monobromodecarboxylated products. These results show that this bromodecarboxylation can be carried out while there is a substituent on the β-position. Besides, *para*-methylcinnamic acid (**1f**) was converted to α-bromolactone (**3**) in only 29% yield and no bromostyrene was found.

Table 1
Results of reactions of **1a** with 1.5 equiv of bromine in different reaction conditions

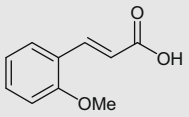
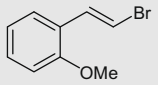
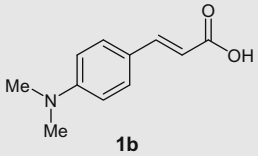
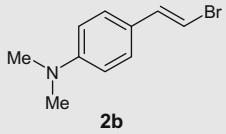
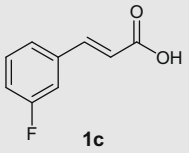
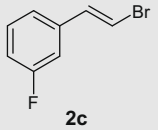
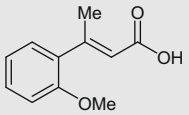
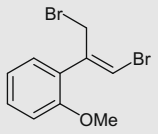
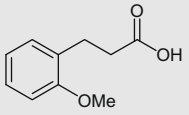
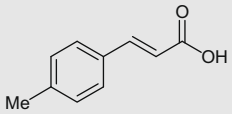
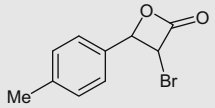
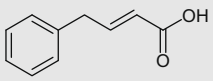
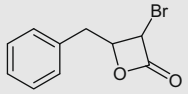
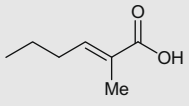
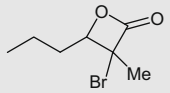
Acetic acid in CH_2Cl_2 (%)	Yield of **2a** (%)
5	62
10	63
20	67
30	60



1a 2a

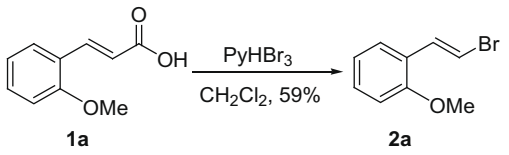
Scheme 1.

Table 2
Results for the reactions of cinnamic acid analogs with bromine

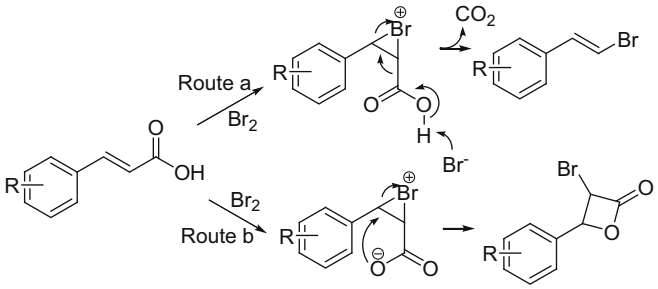
Entry	Substrate	Product	Isolated yield (%)
1	 **1a**	 **2a**	67
2	 **1b**	 **2b**	66
3	 **1c**	 **2c**	81
4	 **1d**	 **2d**	60 (45)[a]
5	 **1e**	Starting material[b]	N/A
6	 **1f**	 **3**	29
7	 **1g**	 **4**	66
8	 **1h**	 **5**	50

[a] The 45% yield was calculated based on the amount of **1e** and 60% yield was obtained based on the amount of bromine used in reaction.
[b] The only identified compound in reaction mixture is the starting material.

In comparison to compound **1a**, 2-hydroxy-cinnamic acid (**6**), a free hydroxyl analog of **1a**, gave a complicated result under the same reaction conditions. Remarkably, 2-hydroxy-cinnamic acid is not completely soluble in CH_2Cl_2 with up to 30% acetic acid, which may hinder this reaction. To confirm that the behavior of **6** was due to its solubility in the solvent, we subjected 3,4-dihydroxyl cinnamic acid (**7**) to the same reaction conditions; this reaction also gave a complicated result. Our findings thus indicate that fluoro, methoxy, and *sec*-amino groups are tolerated under these reaction conditions, but those compounds that are not solu-



Scheme 2.



Scheme 3.

ble in the reaction media (e.g., 2-hydroxy- and 3,4-dihydroxyl cinnamic acid) are not. Furthermore, determination of the olefin configuration from the coupling constant of the two olefinic protons disclosed that all of the reactions gave *trans*-β-bromostyrene. The configuration of **2d** was predicted by comparing C-13 resonance signal of olefin moiety to reported data.[16]

To examine the behavior of an α,β-unsaturated system, and thus gain insight into the reaction mechanism, we subjected 3-(2-methoxyphenyl)propionic acid (**1e**) to the reaction conditions indicated above. When **1e** was treated with bromine, the only identified compound in reaction mixture is starting material. In combination with previous results,[10] the present findings indicate that both the carboxylic acid and olefinic moieties are critical for the conversion of the α,β-unsaturated acid to the corresponding β-bromostyrene.

Furthermore, *E*-4-phenyl-2-butenoic acid (**1g**) was used as the starting material in this reaction. Instead of bromodecarboxylation, bromolactonization occurred and compound **4** was identified as the main product. Meanwhile, reaction of 2-methylhexenoic acid (**1h**) under the same conditions afforded bromo-β-lactone **5**. The similar transformation has been observed.[7c] We propose that **3**, **4**, and **5** were formed via a bromonium intermediate leading to lactonization rather than decarboxylation. The results for these reactions suggest that hyperconjugation of the carboxylic acid, olefin, and phenyl ring is necessary for the bromodecarboxylation and this fact may explain the various observations we have here.

Instead of volatile bromine, pyridine hydrobromide perbromide ($PyHBr_3$), a solid produced according to the literature procedure,[17] was used as bromide source. To the solution of **1a** in CH_2Cl_2 with 10% of AcOH was added $PyHBr_3$ as solid in three portions and 59% of **2a** was collected. This result indicates that bromine can be replaced in this reaction and the application of $PyHBr_3$ makes this approach more convenient and safer (Scheme 2).

Based on the current findings, we propose the reaction mechanism shown in Scheme 3. This reaction begins with the bromination of the olefin to give a bromonium ion intermediate. Ring-opening of this bromonium ion then restores the double bond to form the corresponding *trans*-β-bromostyrene (Route a). Meanwhile, the carboxylate may attack the bromonium ion to form bromolactone (Route b). Although the exact factors affecting the relative favorabilities of these two routes are not clear, the present results indicate that the absence of the salt and the characters of the bromonium ion are important issues. In addition, the formation of the bromonium ion could shed light on the influence of the substituent on the phenyl ring in this reaction.

In conclusion, a convenient single-step protocol for synthesizing β-bromostyrene has been described. This reaction yields the desired compounds in moderate to good yield for reactants with various substituents except *p*-methyl and hydroxyl group. Based on current results, an olefin, phenyl ring, or carboxylic acid is a necessary structural moiety for this type of conversion. In comparison to previous finding, this protocol uses only 10% of acetic acid and no salt is necessary in this reaction. In this study, we also find the requirement of formation of β-lactone or vinyl bromide. Furthermore, the solubility of the starting material in the reaction medium is a critical factor. Moreover, $PyHBr_3$ was proven as good agent to replace bromine in this reaction. We are currently studying the scope and limitations of this reaction with other substituted cinnamic acids and heterocyclic analogs as well as with different halogenated agents.

Representative procedure: To a solution of 2-methoxycinnamic acid (**1a**, 0.5 g, 2.8 mmol) in a mixture of CH_2Cl_2 (18 mL) and acetic acid (2 mL) was added a solution of bromine (0.1 M, 1.5 equiv) in CH_2Cl_2 (40 mL) dropwise at 0 °C. After addition, the reaction was stirred at the same temperature for an additional 1 h. To consume the excess bromine, cyclohexene (5 mL) was added to the reaction mixture and the mixture was stirred for a further 30 min. After removal of solvent, the resulting mixture was partitioned between H_2O and CH_2Cl_2. The organic extracts were washed with water, brine, and dried (Na_2SO_4). Evaporation of the solvent followed by chromatography of the residue over silica gel (Hex/EA = 30:1) afforded the desired compound **2a**. ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.88 (dd, 1H, J = 8, 1 Hz), 6.91 (d, 1H, J = 14 Hz), 6.93 (dd, 1H, J = 8, 1 Hz), 7.24–7.29 (m, 2H), 7.31 (d, 1H, J = 14 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 107.9, 111.0, 120.7, 124.8, 128.0, 129.3, 133.0, 156.6. HRMS: calcd for C_9H_9BrO: 211.9837; found 211.9839.

Acknowledgments

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