

## Accepted Manuscript

Transition metal free large-scale synthesis of aromatic vinyl chlorides from aromatic vinyl carboxylic acids using bleach

Navnath T Hatvate, Balaram S. Takale, Shrikant M. Ghodse, Vikas N. Telvekar

PII: S0040-4039(18)31124-9  
DOI: <https://doi.org/10.1016/j.tetlet.2018.09.034>  
Reference: TETL 50273

To appear in: *Tetrahedron Letters*

Received Date: 20 July 2018  
Revised Date: 4 September 2018  
Accepted Date: 13 September 2018

Please cite this article as: Hatvate, N.T., Takale, B.S., Ghodse, S.M., Telvekar, V.N., Transition metal free large-scale synthesis of aromatic vinyl chlorides from aromatic vinyl carboxylic acids using bleach, *Tetrahedron Letters* (2018), doi: <https://doi.org/10.1016/j.tetlet.2018.09.034>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

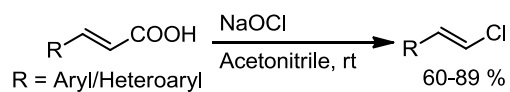


## Graphical Abstract

**Transition metal free large-scale synthesis of aromatic vinyl chlorides from aromatic vinyl carboxylic acids using bleach**

Leave this area blank for abstract info.

Navnath T. Hatvate, Balaram S. Takale, Shrikant M. Ghodse and Vikas N. Telvekar\*



- ◆ Mild reaction conditions
- ◆ Transition-metal free
- ◆ Operationally simple
- ◆ Easily accessible starting materials



ELSEVIER

Tetrahedron Letters  
journal homepage: www.elsevier.com

## Transition metal free large-scale synthesis of aromatic vinyl chlorides from aromatic vinyl carboxylic acids using bleach

Navnath T Hatvate<sup>a</sup>, Balaram S. Takale<sup>b</sup>, Shrikant M. Ghodse<sup>a</sup> and Vikas N. Telvekar<sup>a\*</sup>

<sup>a</sup> Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Matunga (E), Mumbai 400 019, Maharashtra, India

<sup>b</sup> Department of Chemistry and Biochemistry, University of California, Santa Barbara 93106, USA

### ARTICLE INFO

#### Article history:

Received

Received in revised form

Accepted

Available online

#### Keywords:

Acids

Chlorides

$\alpha,\beta$ -unsaturated

Decarboxylation

Hypochlorite

### ABSTRACT

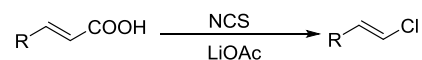
While continuing our research on Hunsdiecker reaction, we came across an interesting application of *bleach*, sodium hypochlorite (NaOCl) for decarboxylative chlorination reaction. The reaction is easily scaled up to 10 mmol. The reaction has good tolerance towards wide variety of functional groups. The reaction has mild conditions and gave relatively high chemical yield of the desired product.

2009 Elsevier Ltd. All rights reserved.

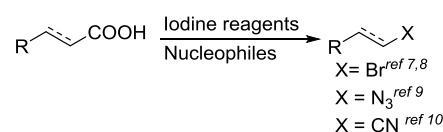
Vinyl halides have potential applications as building blocks for variety of reactions.<sup>1</sup> The well-known basic reaction to prepare halides from carboxylic acids by subsequent loss of carbon dioxide is Hunsdiecker reaction.<sup>2</sup> However, extreme moisture sensitive nature of silver salts of carboxylate had led to number of modifications.<sup>3</sup> Hunsdiecker reaction could also be used to prepare vinyl halides from  $\alpha, \beta$ -unsaturated acid. However, a classical Hunsdiecker reaction for the preparation of unsaturated halides is not easy or effective, hence results in poor chemical yields, and also requires high reaction temperature (ca. 60 °C) which influences the stereochemistry along the double bond.<sup>4</sup> Very nice study on decarboxylation of unsaturated acid by Chowdhury et al., suggested that N-halo-succinamide could be used as a reagent for obtaining vinyl halides at room temperature in comparatively higher chemical yields. There are very few other protocols for this purpose (Scheme 1).<sup>5</sup> The potential drawback of using N-halo-succinamide lies in the fact that, equivalent amounts of succinamide is left in the reaction mixture which causes separation issues. Moreover, it also requires lithium acetate or TBAFA (Tetrabutylammonium trifluoroacetate) as a catalyst, and reactions scales were not optimized towards preparative scales (multi-grams scales). Solas et al., used hypochlorous acid under cryogenic conditions to prepare chlorolactones like **b** shown in Scheme 2. These lactones could then thermally decompose to vinyl chlorides. However, the generality for the synthesis of vinyl chlorides was not shown.<sup>6</sup> In addition to these methods, we took an advantage of mild reaction

conditions provided by hypervalent iodine reagent for decarboxylative bromination of  $\alpha, \beta$ -unsaturated acid.<sup>7</sup> Another attempt using the combination of HBr and NaNO<sub>2</sub> was successful.<sup>8</sup> Further, we were also able to apply decarboxylation technology using other nucleophiles such as azide.<sup>9</sup> Additionally, decarboxylative cyanation of aliphatic carboxylic acid was achieved.<sup>10</sup> However, we were not able to avoid the use of iodine reagents (hypervalent iodine reagents generate equivalent amounts of organoiodine byproducts in the reaction), and also our success in halo-decarboxylation was limited to decarboxylative brominations.

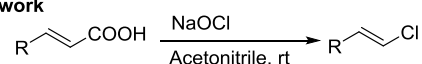
#### 1. State of the art<sup>ref 5</sup>



#### 2. Our previous work



#### 3. This work



**Scheme 1.** State of the art, our previous attempts, and current work for decarboxylation reactions.

\* Corresponding author. Tel.: +91-22-3361-2219; e-mail: [vn.telvekar@ictmumbai.edu.in](mailto:vn.telvekar@ictmumbai.edu.in);

Continuing this research, our initial attempt to prepare vinyl chloride from vinyl carboxylic acid using sodium hypochlorite in dimethyl sulfoxide led to poor yield. Nevertheless, we considered it as a starting point for an optimization study. This technique is applied to different substrates and results of decarboxylative chlorination are presented here.

To start, 10 mmol of cinnamic acid **1a** was stirred at room temperature for 8 h with 1 equiv. of NaOCl in DMSO (Note: commercially available 9-12% chlorine basis NaOCl solution was used throughout this study, see supporting information). To our surprise, 20% yield of the desired product was obtained (Table 1, entry 1). Different solvents were studied for this reaction from which acetonitrile proved to be the best and resulted in 30% yield of the desired vinyl chloride (entry 2). To get hike in the chemical yield, different stoichiometric ratios of sodium hypochlorite were studied, and found that 5 equivalents of sodium hypochlorite was required to give maximum chemical yield (entry 5). Increasing the reaction temperature exerted negative effect on the yield (entry 8). Probably due to decomposition of hypochlorite. Finally, *t*-BuOCl was found to give similar yield of the desired product, but NaOCl was chosen for further study owing to its easy availability, and bad reaction profile of *t*-BuOCl (entry 9). To make this protocol greener, water was used as a solvent, but yield decreases due to insolubility of starting material in water (entry 10).

**Table 1.** Optimization for the synthesis of vinyl chloride **2a**<sup>a</sup>

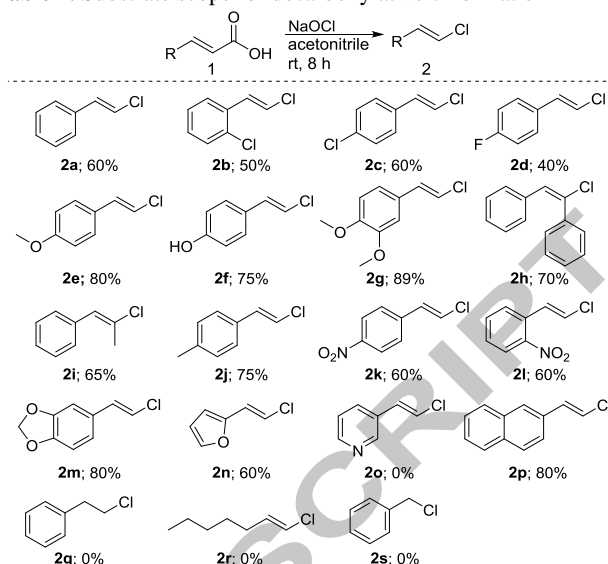
Entry	Reagent (equiv)	Solvent	Yield (%) <sup>b</sup> of <b>2a</b>
1	NaOCl (1)	DMSO	20
2	NaOCl (1)	Acetonitrile	30
3	NaOCl (2)	Acetonitrile	45
4	NaOCl (3)	Acetonitrile	50
5	NaOCl (5)	Acetonitrile	60
6	NaOCl (6)	Acetonitrile	60
7	NaOCl (5)	DMSO	55
8	NaOCl (5)	Acetonitrile	55 <sup>c</sup>
9	<i>t</i> -BuOCl (1)	Acetonitrile	61 <sup>d</sup>
10	NaOCl (5)	Water	trace <sup>e</sup>

<sup>a</sup>Reaction conditions: 10 mmol of **1a**, 50 mmol of NaOCl, stirred in 15 mL of solvent at rt for 8 h. <sup>b</sup>Isolated yield. <sup>c</sup>Reaction temperature was 50 °C.

<sup>d</sup>Reaction was messy. <sup>e</sup>Cinnamic acid was not completely soluble in water.

The optimized conditions were then applied on various substrates (Table 2). Almost all of the  $\alpha$ ,  $\beta$ -unsaturated carboxylic acids resulted in satisfactory chemical yields of the desired products considering their reaction scale (entries **2a** to **2o**). Interesting to know that, halo substitution was tolerated (entries **2b-2d**), although low yield in the case of 4-fluorocinnamic acid was observed. Radical oxidation of methyl group from **2i** or **2j** was not observed nor the aromatic chlorination of any other substrate or product.<sup>11, 12</sup> Presence of strong electron withdrawing groups on aryl ring were also found to give satisfactory chemical yields (entries **2k** and **2l**). Heterocyclic substituted acrylic acid gave good chemical yield of the corresponding vinyl chloride (entry **2n**). However, 3-pyridineacrylic acid could not give the desired product (entry **2o**).

**Table 2.** Substrate scope for decarboxylative chlorination<sup>a</sup>



<sup>a</sup>Reaction conditions: 10 mmol of **1a**, 50 mmol of NaOCl, stirred in 15 mL of solvent at rt for 8 h (entries in boldface represents isolated yields).

Similarly, 2-heptenoic acid was unable to give the desired heptenyl chloride **2r**. Requirements of unsaturated acid is confirmed by treating saturated cinnamic acid (dihydrocinnamic acid; **1q**) with current conditions but did not give the product **2q**. Similar reactivity trend is observed when benzylic acid such as phenyl acetic acid (entry **1s**) was used, and no desired product **2s** was formed. This suggested that substrates should have  $\alpha$ ,  $\beta$ -unsaturated acid component to undergo decarboxylative chlorination. The mechanism predicted in Scheme 2 partly supports this phenomenon.

We were curious to know why further aromatic chlorination after decarboxylative chlorination of either product or substrate is not occurred in our reaction conditions, which is otherwise difficult to avoid.<sup>11, 12</sup> Hence, along with vinyl chloride **2a**, we exposed few selected substrates to current optimized condition. It was interesting to know that, even exposing vinyl chloride **2a** with NaOCl, no further chlorination of either aryl or alkenyl group was observed. Benzoic acid was found to be inert and did not give any product. However, methyl benzoate was hydrolyzed to benzoic acid in 20% yield, while benzyl alcohol was oxidized to benzaldehyde in 50% yield. Aliphatic chlorination of nitrotoluene was not occurred with current condition. Alkene such as stilbene was quite inert and did not result in any oxidation or epoxidation of double bond.<sup>13</sup> From this study, it is clear that the reaction has wide functional group tolerance even if sodium hypochlorite has known to do aromatic or aliphatic chlorination.<sup>11, 12</sup> However, we should also mention here that ester and alcohols are not tolerated in current reaction condition.

**Table 3.** Functional group tolerance towards optimized conditions<sup>a</sup>

Entry	Substrate	Product	Yield (%) <sup>b</sup>
1	<b>2a</b>	NR <sup>c</sup>	--
2		NR <sup>c</sup>	--
3		Benzoic acid	20
4		Benzaldehyde	50
5		NR <sup>c</sup>	--
6		NR <sup>c</sup>	--

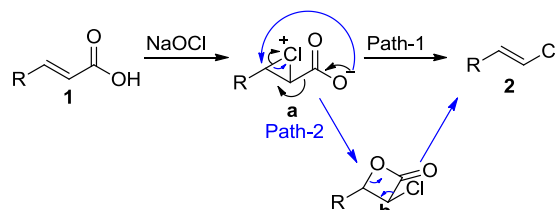
<sup>a</sup>Reaction conditions: 10 mmol of Substrate, 50 mmol of NaOCl, stirred in 15 mL of acetonitrile at rt for 8 h. <sup>b</sup>Isolated yield. <sup>c</sup>NR: No Reaction (starting material, substrate recovered quantitatively).

To prepare more reactive vinyl halides, we tried few one-pot shuttling experiments using molecular iodine and bromine (Table 4). It should be noted that, halide shuttling occurred while reaction progresses and not after it's done. For example, addition of I<sub>2</sub> or Br<sub>2</sub> initially along with NaOCl resulted in the formation of vinyl iodide or bromide respectively (entries 1 and 4), while the same was not observed when these molecular halides were added after completion of the reaction, which means halogen exchange could not be achieved in this reaction system (entries 2 and 5). However, it is also difficult to say how vinyl halides were formed in these reactions, because separate reaction of vinyl carboxylic acid with molecular I<sub>2</sub> resulted in 20% yield of the desired product **3a** (entry 3) but use of Br<sub>2</sub> did not give any vinyl bromide **4a** (entry 6). This rather suggests that direct *decarboxylative iodination can be done* using I<sub>2</sub> in the absence of sodium hypochlorite, however *decarboxylative bromination could not be done* only by using Br<sub>2</sub>.

**Table 4.** Halide shuttling experiments<sup>a</sup>

Entry	X <sub>2</sub>			
		Yield <sup>b</sup> of <b>2a</b> (%)	Yield <sup>b</sup> of <b>3a</b> (X = I) (%)	Yield <sup>b</sup> of <b>4a</b> (X = Br) (%)
1	I <sub>2</sub>	31	24	--
2 <sup>c</sup>	I <sub>2</sub>	55	0	--
3 <sup>d</sup>	I <sub>2</sub>	0	20	--
4	Br <sub>2</sub>	47	--	18
5 <sup>c</sup>	Br <sub>2</sub>	49	--	0
6 <sup>d</sup>	Br <sub>2</sub>	0	--	0

<sup>a</sup>Reaction conditions: 10 mmol of **1a**, 50 mmol of NaOCl, 10 mmol of I<sub>2</sub>/Br<sub>2</sub> stirred in 15 mL of acetonitrile at rt for 8 h. <sup>b</sup>Isolated Yield. <sup>c</sup>Either I<sub>2</sub> or Br<sub>2</sub> was added after 8 h. <sup>d</sup>Separate reaction in the absence of NaOCl but in the presence of I<sub>2</sub> (entry 3) or Br<sub>2</sub> (entry 6).

**Scheme 2.** Predicted reaction pathway for decarboxylative chlorination.

Based on current experiments and previous literature,<sup>6</sup> a probable reaction pathway is predicted in Scheme 2. vinyl carboxylic acid **1** reacts with hypochlorite to form chloronium ion **a** which can either undergo direct concerted decarboxylation to the corresponding vinyl chloride **2** (Path 1) or it can form a 4 membered chloropropiolactone, **b** and the later can undergo decarboxylation to the product **2** (Path 2).

## Acknowledgments

VNT thanks to University Grant Commission, New Delhi, India for providing financial support under UGC-Major research scheme. NTH and SMG thank to University Grant Commission, New Delhi, India for providing fellowship under basic science research (UGC-BSR).

## References and notes

- (a) Ding J.; You, Y.; Weng Z. *Tetrahedron Lett.* **2016**, *57*, 1724. (b) Tang J.; Gooßen L. J. *Org Lett.* **2014**, *16*, 2664. (c) Li, M.; Gutierrez, O.; Berritt, S.; Pascual-Escudero, A.; Yeşilçimen, A.; Yang, X.; Adrio, J.; Huang, G.; Nakamaru-Ogiso, E.; Kozłowski, C.; Walsh P.J. *Nat Chem.* **2017**, *9*, 997. (d) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315.
- (a) Johnson, R.; Ingham, R. T. *Chem. Rev.* **1956**, *66*, 219. (b) Wilson, C. V. *Org. Reactions*, **1957**, *9*, 332.
- (a) Cristol, S. J.; Firth Jr., W. C. *J. Org. Chem.* **1961**, *26*, 280. (b) Cristol, S. J.; Gaston, L. K.; Tiedeman, T. J. *J. Org. Chem.* **1964**, *29*, 1279. (c) Davis, J. A.; Herynk, J.; Carroll, S.; Johnson, D. Bunds. J.; *J. Org. Chem.* **1965**, *80*, 415.
- Graven, A.; Jorgensen, K.A.; Dahl, S.; Stanczak, A. *J. Org. Chem.* **1994**, *59*, 3543.
- (a) Chowdhury, S.; Roy S. *J. Org. Chem.* **1997**, *62*, 199. (b) Naskar, D.; Chowdhury, S.; Roy, S. *Tetrahedron Lett.* **1998**, *39*, 699. (c) Kuang, C.; Senboku, H.; Tokuda, M. *Synlett.* **2000**, *10*, 1439.
- Solas, D.; Wolinsky, J. *Synth. Commun.* **1981**, *11*, 609.
- Telvekar, V. N.; Arote, N. D.; Herlekar, O. P. *Synlett.* **2005**, 2495.
- For decarboxylative bromination, see; Telvekar V. N.; Takale, B. S. *Tetrahedron Lett.* **2011**, *52*, 2394.
- For decarboxylative azidation, see; Telvekar V. N.; Takale, B. S.; Bachhav H. M. *Tetrahedron Lett.* **2009**, *50*, 5056.
- For decarboxylative cyanation, see; Telvekar V. N.; Rane R.A. *Tetrahedron Lett.* **2007**, *48*, 6051.
- For aromatic chlorination using hypochlorite, see; Smith, J. C. *J. Chem. Soc.* **1934**, 213.
- For benzylic oxidation, see; Jin, C.; Zhang L.; Su, W. *Synlett.* **2011**, 1435.
- For oxidation of double bond using NaOCl, see; (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (b) Mehlretter, G. M.; Bhor, S.; Klawonn, M.; Döbler, C.; Sundermeier, U.; Eckert, M.; Militzer, H.-C.; Beller, M. *Synthesis*, **2003**, 295.

## Highlights:

1. Transition metal free approach is compatible with aromatic/heteroaromatic vinyl carboxylic acid.
2. Mild reaction condition for synthesis of vinyl chloride.
3. Simple Cinnamic acids is the starting material.
4. Applicable to gram-scale synthesis.

ACCEPTED MANUSCRIPT