Tetrahedron Letters 58 (2017) 2842–2845

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Chloro/bromotrimethylsilane-$Cu(NO_3)_2{\cdot}3H_2O$: Safe and efficient reagent system for the decarboxylative *ipso*-nitration and dibromination of cinnamic acids

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ARTICLE INFO

Article history:
Received 16 May 2017
Accepted 6 June 2017
Available online 8 June 2017

Keywords:
ipso-Nitration
Cinnamic acid
β-Nitrostyrenes
Halotrimethylsilane
Copper(II) nitrate

ABSTRACT

Further synthetic potential of halotrimethylsilane-nitrate salt mixture is revealed. A mixture of TMSX-$Cu(NO_3)_2{\cdot}3H_2O$ system is found to be an efficient reagent system for both the decarboxylative nitration (*ipso*-nitration) when X = Cl, and dibromination of cinnamic acids, with X = Br, under mild conditions. The reactions are safe and simple, affording the corresponding products (*E*)-*β*-nitrostyrenes, and *anti*-2,3-dibromo-3-phenylpropanoic acids in high yields with high selectivity in a relatively short time. Use of hazardous and toxic nitrating systems such as acetyl nitrate and brominating agents such as molecular bromine can be avoided.

Introduction

A suitable combination of nitrate salts and trimethylsilyl halides forms an efficient reagent system, which has been successfully used in various organic synthetic transformations such as nitration of aromatics and olefins,[1] oxidative nitration of olefins to 2-nitroketones,[2] deoximation of aldoximes/ketoximes,[3] non-aqueous diazotization etc.[4] During our studies on the *ipso*-substitution of arylboronic acids, we reported that a mixture of nitrate salt and chlorotrimethylsilane (TMSCl) is an effective and highly selective nitrating agent for the *ipso*-nitration of arylboronic acids.[5] This combination was later found to be an effective reagent system for the oxidation of sulfides/sulfoxides,[6a] oxidative chlorination of thiols/disulfides,[6a] and *α*-chlorination of acetophenones.[6b] Similarly, *ipso*-nitrosation of arylboronic acids was achieved using TMSCl-nitrite salt combination.[6c] Such promising results obtained by employing metal nitrates and trimethylsilyl halides motivated us to further explore the scope and generality of this reagent system in achieving the preparation of nitroolefins from *α*,*β*-unsaturated carboxylic acids. Synthesis of nitroolefins has been one of the most extensively studied[7] reactions as they are building blocks of many useful biological and pharmaceutical compounds, and are widely used as intermediates in many reactions such as Michael reaction,[8] Diels-Alder reaction,[9] Friedel-Crafts alkylation[10] etc. Consequently, the efficacy in synthesizing such compounds is of great importance in organic chemistry.

Nitroolefins can be conventionally obtained from the Henry reaction[11,12] or could be synthesized from *α*,*β*-unsaturated carboxylic acids by employing nitric acid[13–15] or gaseous nitrogen dioxide[16] as a NO_2 source. Alternative methods for synthesizing nitroolefins include employing *tert*-butyl nitrite[17–19] and transition metal salts such as silver(I) nitrite[20] in conjunction with TEMPO, iron(III) nitrate[21,22] and cerium(IV) ammonium nitrate (CAN).[23] The latter methods have reportedly been used to achieve a better yield, avoiding harsh conditions, and other difficulties associated with handling gaseous reagents. However, there are limitations associated with the use of such methods due to the cost as well as toxic nature of some of the reagent components. Therefore, we searched for more economically viable and safer reagent system. We developed the present protocol intrigued by recently reported nitration of cinnamic acids using anhydrous copper(II) nitrate.[24] We realized that anhydrous $Cu(NO_3)_2$ is not easily commercially accessible and drying the hydrate $Cu(NO_3)_2{\cdot}3H_2O$ is not safe and results in decomposition to NO_2 and CuO. The reported reaction was shown to be affording good yields only with cinnamic acid derivatives bearing electron donating groups in the ring. Since the mechanism shown is ambiguous, we decided to carry out the reaction with $Cu(NO_3)_2{\cdot}3H_2O$, which is commercially available and make the reaction more feasible and practically applicable. When the reaction of cinnamic acid was conducted with

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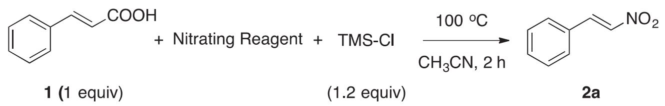
http://dx.doi.org/10.1016/j.tetlet.2017.06.017

Table 1
Effect of Various Nitrate Salts on the *ipso*-Nitration of Cinnamic Acid.



Entry	Nitrate Salts	Conversion (%)[a]
1	$Bi(NO_3)_3{\cdot}5H_2O$ (3equiv)	No reaction
2	$NaNO_3$ (6 equiv)[b]	45
3	KNO_3 (6 equiv)[b]	20
4	NH_4NO_3 (3 equiv)	Trace
5	$Zn(NO_3)_2{\cdot}xH_2O$ (3 equiv)	3
6	$Ni(NO_3)_2{\cdot}6H_2O$ (3 equiv)	13
7	$AgNO_3$ (3 equiv)	100
8	$Cu(NO_3)_2{\cdot}3H_2O$ (3.5 equiv)	100

[a] Conversion obtained by GC–MS analysis.
[b] The reactions were conducted at both 50 °C and 100 °C and many side products were observed.

$Cu(NO_3)_2{\cdot}3H_2O$ alone, the desired *ipso*-nitration reaction did not occur smoothly as expected. Interestingly, in a very recent paper, Nenajdenko et al.[25] detailed the *ipso*-nitration of β-bromostyrenes in high yield with *Z*-selectivity using $Fe(NO_3)_3{\cdot}9H_2O$ in excess, in which NO_2 radical formed in situ is the nitrating species. While they used $Cu(NO_3)_2{\cdot}3H_2O$, they could achieve the product only in 40–55% yield. Based on the protocol for the *ipso*-nitration of arylboronic acids using TMSX-metal nitrate combination reported by us a decade ago,[5] we decided to apply a similar strategy to solve this problem. Herein, we report a simple, economic, and highly efficient method for the decarboxylative nitration (*ipso*-nitration) of cinnamic acids that affords (*E*)-β-nitrostyrenes in good to excellent yields. The reaction is feasible with cinnamic acids with both electron donating and electron withdrawing groups in the ring. Also, by using excess amount of bromotrimethylsilane (TMSBr) and much lower amount of the nitrate salt, synthesis of the corresponding *anti*-2,3-dibromo-3-phenylpropanoic acids was achieved in excellent yields, avoiding the use of molecular bromine or other hazardous brominating agents. Therefore, the presence of appropriate halotrimethylsilane makes the reaction safe and efficient.

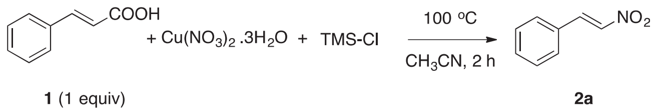
In order to find the most cost effective and efficient nitrating agent, a series of different nitrate salts was screened in the presence of TMSCl using cinnamic acid for the *ipso*-nitration (Table 1). The reaction mixture was stirred for 2 h at 100 °C and analyzed by GC–MS. Since bismuth(III) nitrate was shown to be an efficient *ipso*-nitrating agent for the *ipso*-nitration of arylboronic acids,[26] we conducted the reaction initially with bismuth(III) nitrate. While bismuth(III) and ammonium nitrates did not lead to the desired product, small amount of the nitro product was observed when zinc(II) nitrate or nickel(II) nitrate was employed. However, sodium nitrate and potassium nitrate gave 20% and 45% conversion respectively, which could not be improved much with further attempts. Interestingly, when silver(I) nitrate and copper(II) nitrate were employed, quantitative conversion to the desired product was observed. However, being less expensive, $Cu(NO_3)_2{\cdot}3H_2O$ was chosen as the nitrating agent of choice for further studies of the *ipso*-nitration of cinnamic acids.

Optimization of the reaction conditions was carried out by conducting reactions of cinnamic acid in dry acetonitrile at 100 °C and monitoring the progress of the reaction by GC–MS (Table 2). Based on the GC–MS data, we found that benzaldehyde was formed as a side product, which was minimized by increasing the amount of $Cu(NO_3)_2{\cdot}3H_2O$. After a series of trials, by using 3.5 equivalents of $Cu(NO_3)_2{\cdot}3H_2O$, we were able to achieve quantitative conversion of cinnamic acid to β-nitrostyrene without the formation of benzaldehyde (entry 6, Table 2).

Although three equivalents of $Cu(NO_3)_2{\cdot}3H_2O$ gave an excellent conversion (99%), the conditions of entry 6 in Table 2 were chosen as it led to the formation of the product in almost pure form. By simple aqueous workup followed by extraction and evaporation of the solvent, the product could be easily isolated in pure form without further purification. To explore the necessity of TMSCl as the reagent partner, a few reactions were also carried with varying amounts of TMSCl. Lower amounts of TMSCl resulted in slight decline in the yield of the desired product (Table 2, entry 7–8). However, when the reaction was conducted in the absence of TMSCl, the conversion sharply dropped to 18% (Table 2, entry 9), clearly demonstrating the crucial role of TMSCl in improving the efficacy of the reactions significantly (Table 2).

The efficiency of this method was further explored by conducting the reactions of different derivatives of cinnamic acids under the optimized conditions. The results summarized in Table 3 reveal that the chlorotrimethylsilane-copper(II) nitrate reagent system affords desired products in good to excellent yields not only for the substrates with electron rich substituents (**2b, 2j**), but also for those with highly electron withdrawing groups (**2c, 2h**). Similarly, in the case of halogenated substrates also, we were able to obtain excellent yields (**2e-g**). To the best of our knowledge, among all methods of *ipso*-nitration of

Table 2
Optimization of the Reaction Conditions.



Entry	$Cu(NO_3)_2{\cdot}3H_2O$ (equiv)	TMSCl (equiv)	Conversion (%)[a]		
			1	**2a**	PhCHO
1	1.2	1.2	0	95	5
2	1.9	1.2	0	96	4
3	2.2	1.2	0	96	4
4	2.5	1.2	0	97	3
5	3.0	1.2	0	99	1
6	3.5	1.2	0	100	0
7	3.5	0.9	0	98	1
8	3.5	0.6	0	95	2
9	3.5	0	81	18	1

[a] Conversion obtained by GC–MS.