Iranian Journal of Organic Chemistry Vol. 4, No. 4 (2012) 911-915

A mild and simple one-pot procedure for the conversion of aldehydes to methyl esters

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Received: May August; Revised: September 2012; Accepted: October 2012

Abstract: A simple and mild one-pot procedure for the facile direct oxidative methyl esterification of aldehydes using *N*-iodo saccharine with K_2CO_3 in methanol is described. Several methyl esters were obtained using this procedure from the corresponding aldehydes in high to excellent yields.

Keywords: One-Pot, Esterification, Methyl ester, *N*-Iodo saccharine, Aldehyde.

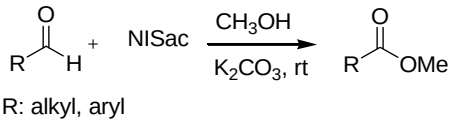
Introduction

Esters are immensely important organic compounds due to their application in a wide range of industrial products such as plasticizers, graphics, lubricants, flavours, perfumes and cosmetics [1]. Thus, the synthesis of carboxylic esters is one of the most fundamental and pivotal protocols for producing natural and synthetically useful compounds in organic chemistry [2].

The direct oxidative esterification of aldehydes to esters is an extremely useful in organic synthesis [3]. A two-step reaction sequence involving the oxidation of hemiacetal [4], acetal [5] or cyanohydrin [6] can bring this conversion. Several one-pot conversions using different transition metal oxidants such as pyridinium dichromate [7], MnO_2 [8], methyltrioxorhenium [9], oxone [10], SnO_2/SBA-1-H_2O [11], Rhodium [12] and expensive silver [13] have been reported. The other oxidative esterification protocol uses halogen derived oxidants such as *N*-halosuccinimide [14], hypochlorites [15], pyridiniumhydrobromide perbromide [16] and molecular bromine [17]. Despite these intensive efforts for oxidative esterification of aldehydes, the development of a more effective and mild method still remains interesting since many of the known methods require toxic heavy metal oxidants, dry reaction conditions, long reaction time and poor yields of the products.

N-Halosaccharins (NXSac, X = Cl, Br, I) are stable crystalline compounds, soluble in most common organic solvents and insoluble in water [18a, 19] and more electrophilic than their analogues such as *N*-haloamides. *N*-halosaccharins can be used as oxidants in the organic reactions such as oxidation of (*p*-substituted phenylthio) acetic acids and alcohols [20] and they are often employed for the halogenation of alkenes, activated aromatic compounds, enol acetates, 1,3-diones and etc. [19,21].

Herein, we report an efficient method for oxidative esterification of a variety of aldehydes with methanol in the presence of *N*-iodosaccharin in combination with K_2CO_3 as a base at room temperature (Scheme **1**).



R: alkyl, aryl

Scheme 1: Conversion of aldehydes to methyl esters in the presence of *N*-iodosaccharin

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Results and discussion

To study of oxidative esterification process, we have examined benzaldehyde as a model compound. When benzaldehyde (1 mmol) was stirred in methanol (10 ml) in the presence of *N*-iodosaccharine (2.60 mmol) and K_2CO_3 (4 mmol) at room temperature, after 75 min methyl benzoate was obtained in 93% yield (Table **1**, entry 1).

The potential scope of this oxidative esterification was then extended to a range of various aromatic, heteroaromatic and aliphatic aldehydes. The results are shown in Table **1**.

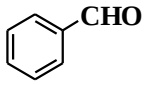
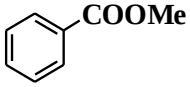
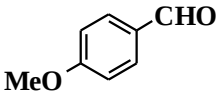
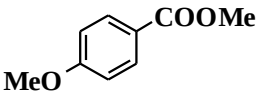
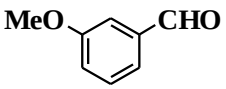
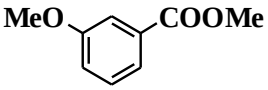
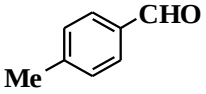
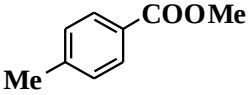
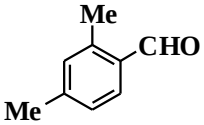
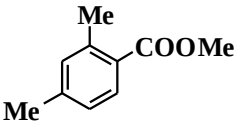
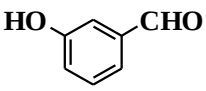
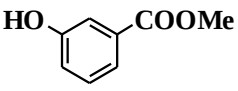
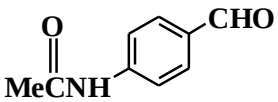
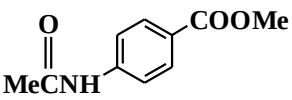
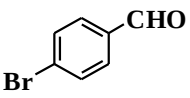
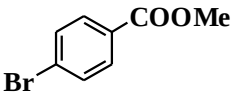
The reactions well proceed in spite of an electron-donating substituents, a methoxy, methyl, hydroxyl and acetamido group and underwent a clean oxidative esterification to form corresponding methyl esters (entries 2–7). Similarly, other aromatic aldehydes with electron-withdrawing substituents underwent oxidative methyl esterification in good to excellent yields (Table **1**, entries 8-11).

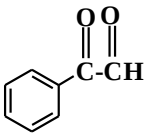
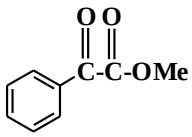
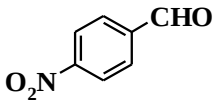
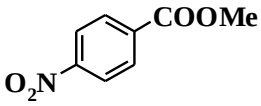
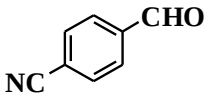
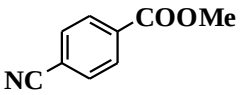
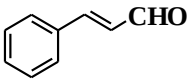
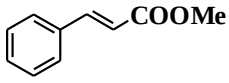
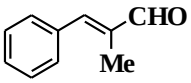
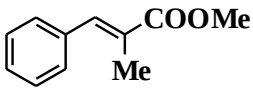
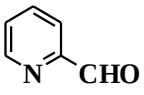
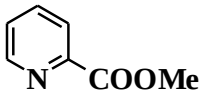
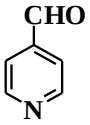
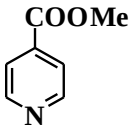
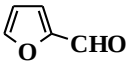
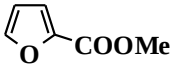
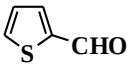
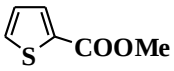
The reaction of cinnamaldehyde and α-methyl cinnamaldehyde with NISac in methanol produce exclusively corresponding methyl cinnamate in 90% and 70% yield respectively without any observable reaction at the double bond functionality (Table **1**, entries 12, 13).

The hetroaromatic aldehydes such as pyridine, furan and thiophen aldehyde also give the desired compounds without any problem (Table **1**, entries 14-17). Finally, the aliphatic aldehydes (entries 18, 19) also gave the corresponding methyl esters in high yields.

It is important to note that iodination product of any aromatic aldehydes was not observed under the above reaction conditions as well as in methanol as reaction solvent.

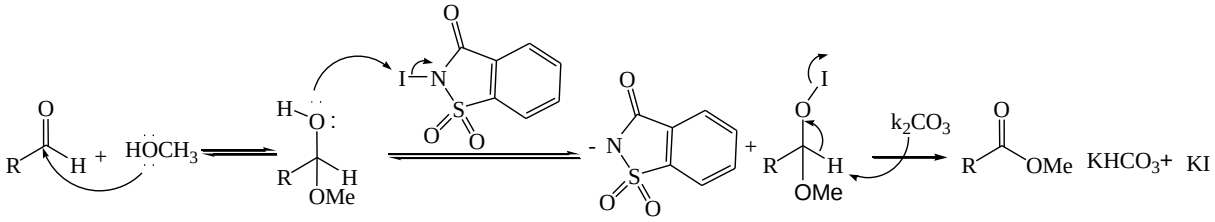
Table 1: Oxidative methyl esterification of aldehydes using NISac[a]

Entry	Substrate	Product	Time(min)	Yield (%)	Ref.
1			75	93	22
2			180	87	22
3			30	90	23
4			150	85	22
5			180	80	24
6			120	80	25
7			100	95	26
8			15	95	27

9			8	80	28
10			4	97	22
11			5	97	27
12			120	90	22
13			120	70	22
14			25	85	29
15			25	93	29
16			120	95	30
17			120	85	31
18	$CH_3(CH_2)_2CHO$	$CH_3(CH_2)_2COOMe$	60	87	22
19	$CH_3(CH_2)_4CHO$	$CH_3(CH_2)_4COOMe$	60	87	22

[a]The reaction was carried out under a nitrogen atmosphere and room temperature, using aldehyde (1 mmol), NISac (2.60 mmol), MeOH (10 mL), K_2CO_3 (4 mmol).

As shown in Table **1**, electron-donating groups decrease the rate of esterification reaction, while electron-withdrowing groups increase the reaction rate. A reaction pathway is proposed [14b] (Scheme **2**).



Scheme 2: Proposed mechanism for conversion of aldehydes to methyl esters in the presence of *N*-iodosaccharin

Conclusion

In conclusion a simple, mild, efficient and high yielding method has been developed for the oxidative esterification of aldehydes using NISac and K_2CO_3 in methanol. Various aromatic, hetroaromatic and aliphatic aldehydes were compatible to the reaction conditions.The main advantage of this reaction is the mild conditions, high to excellent yield and one-pot protocol.

Saccharin, which is an edible, non-toxic, commercially available and a cheap material is produced in the reaction mixture can be isolated and halogenated easily for reusing in the similar reactions.

Experimental

Materials were purchased from Fluka and Merck companies. NISac were prepared according to the reported procedure [18b]. Products were characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR and IR) and physical properties and comparison with authentic samples.

General Procedure for the Oxidation of aldehydes with NISac:

To a solution of adehyde (106 mg, 1 mmol) in methanol (10 mL) were added NISac (897 mg, 2.60 mmol) and K_2CO_3 (552 mg, 4 mmol). The resultant dark mixture was stirred for 75 min under the nitrogen atmosphere and room temperature at which time TLC indicated complete consumption of starting material. Water (5 mL) and $Na_2S_20_3$-$5H_20$ (0.5 g) were added to destroy any remaining NISac or hypoiodite species. The resultant mixture was extracted with 4×10 mL of a solution of 50% ether in hexane. The combined organic extracts were washed with brine (5 mL), and the solvent was removed under reduced pressure and obtained methyl ester as a pure product.

Acknowledgment:

This work supported by Research Grant from University of Mazandaran, Iran.

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