

A mild and convenient oxidative transformation of aldehydes to methyl esters using iodosobenzene in combination with KBr

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DOI: <http://dx.doi.org/10.3998/ark.5550190.p009.267>

Abstract

Oxidation of various aliphatic and aromatic aldehydes with iodosobenzene in combination with potassium bromide in aqueous methanol offers a mild and convenient method for their conversion into the corresponding methyl esters. The method is not straightforward for the synthesis of heteroaryl esters.

Keywords: Organohypervalent iodine(III) reagents, iodosobenzene, oxidation, methyl esters

Introduction

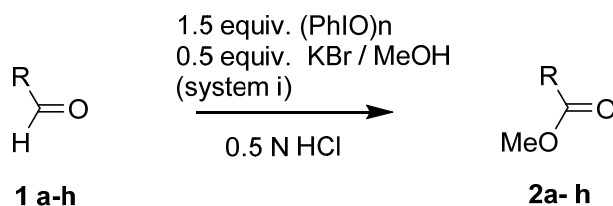
Oxidative transformation of aldehydes (**1**) into esters (**2**) is a very useful reaction in organic synthesis. A number of methods using various reagents have been reported to bring about this transformation (Scheme 1).¹⁻⁹ However, many of these procedures suffer from several limitations such as involvement of toxic heavy metal oxidants, expensive catalyst, large excess of reagents, and dry solvent in inert atmosphere. Furthermore, the requirement of poisonous³ and polluting reagents, mediators, and cocatalysts along with long reaction times and drastic reaction conditions causes severe economic and operational problems. Thus, alternative methods for this transformation are desirable.

Organohypervalent iodine reagents¹⁰⁻¹⁹ have been increasingly used in contemporary organic synthesis. In particular, organoiodine(III) reagents, namely (diacetoxyiodo)benzene,²⁰ bis(trifluoroacetoxy)iodobenzene,²¹ [hydroxy(tosyloxy)iodobenzene]²² and iodosobenzene (IOB)²³ have emerged as versatile oxidizing agents. Organoiodine(III) reagents in combination with other reagents have also shown interesting applications in organic synthesis. For example, Kita *et al.*^{24,25} have reported that iodosobenzene in combination with KBr (*system i*) in aqueous methanol can be employed for the oxidative transformation of alcohols into methyl esters. This reaction has been suggested to proceed through the intermediacy of aldehyde, but these were not isolated. Based on these observations, it was considered worthwhile to examine the oxidation of

aldehydes under similar conditions with a view to develop a facile method for the conversion of aldehydes into esters. Consequently, we report herein a new application of the *system i* for the oxidative conversion of various aldehydes into methyl esters.

Results and Discussion

First, we attempted the oxidation of benzaldehyde (**1d**) with 1.1 equivalent of IOB and KBr (0.2 equivalent) in aqueous methanol according to the reported conditions.^{24,25} However, to our surprise the reaction required more than two days for completion as compared to six hours for conversion of benzyl alcohol to methyl benzoate. The situation was worse when other, substituted benzaldehydes, such as *p*-nitro and *p*-methoxy derivatives were subjected to similar oxidation, most of the starting aldehydes being recovered even after stirring the reaction mixture for 50 hours. After making several attempts, it was found that using a larger amount of methanol leads to considerable increase in conversion of aldehydes **1** to methyl esters **2**. So it became necessary to use methanol in larger amount (see experimental) for all cases.



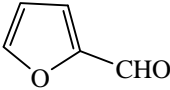
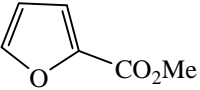
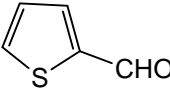
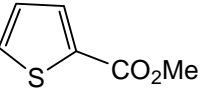
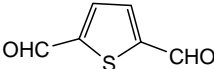
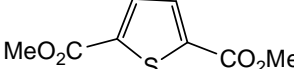
Scheme 1

After optimizing the reaction conditions for benzaldehyde (**1d**), the generality of this methodology was tested by carrying out the oxidation of various aliphatic (**1a-c**) and aromatic (**1e-h**) aldehydes. The method was successful in all cases, and the results are summarized in Table 1.

As expected, the reactions of aromatic aldehydes were slower than aliphatic aldehydes. Further, among aromatic aldehydes, the reactions of those with electron-donating groups at a *para* position gave better results.

When applied to heteroaryl aldehydes, the method was not straightforward in all cases. For example, this approach smoothly converted oxygen and sulfur containing heteroaryl aldehydes such as 2-furancarboxaldehyde (**1i**), 2-thiophenecarboxaldehyde (**1j**) and 2,5-thiophenedicarboxaldehyde (**1k**) into the corresponding methyl esters **2i-2k**. On the other hand, nitrogen-containing heteroaryl aldehydes such as 4-pyrazolecarboxaldehydes on oxidation using *system i* did not afford the desired esters. Instead, a novel C–C bond cleavage was observed. The detailed investigations on the oxidation of various heteroaryl aldehydes are under progress and will be published elsewhere.

Table 1. Oxidative esterification of aldehydes (**1a-h**) with *system i*

Entry	Aldehyde 1	Product 2	Time (h)	Mp (Lit. mp) °C	Yield ^c (%)
1	CH ₃ (CH ₂) ₄ CHO, 1a	CH ₃ (CH ₂) ₄ COOMe, 2a	2	liquid ^a	66
2	CH ₃ (CH ₂) ₆ CHO, 1b	CH ₃ (CH ₂) ₆ COOMe, 2b	2	liquid ^a	70
3	CH ₃ (CH ₂) ₇ CHO, 1c	CH ₃ (CH ₂) ₇ COOMe, 2c	2	liquid ^a	68
4	C ₆ H ₅ CHO, 1d	C ₆ H ₅ COOMe, 2d	5	liquid ^a	90
5	4-ClC ₆ H ₄ CHO, 1e	4-ClC ₆ H ₄ COOMe, 2e	6	42-44 ^b (44) ²⁷	60
6	4-MeC ₆ H ₄ CHO, 1f	4-MeC ₆ H ₄ COOMe, 2f	4	34 ^b (33-36) ²⁷	75
7	4-MeOC ₆ H ₄ CHO, 1g	4-MeOC ₆ H ₄ COOMe, 2g	4	49 ^b (49-51) ²⁷	65
8	4-O ₂ NC ₆ H ₄ CHO, 1h	4-O ₂ NC ₆ H ₄ COOMe, 2h	20	94-96 ^b (96) ²⁷	55
9	 1i	 2i	2	liquid ^a	68
10	 1j	 2j	3	liquid ^a	72
11	 1k	 2k	4	83-84 ^b (82-83) ²⁸	74 ^d

^a Purity of the liquid products was confirmed by tlc and satisfactory elemental analysis (C, H).

^b All these products were finally purified by recrystallization by using minimum amount of methanol. For products **2e**, **2f** and **2g**, the hot solution was slowly cooled to room temperature and then left in refrigerator for few hours.

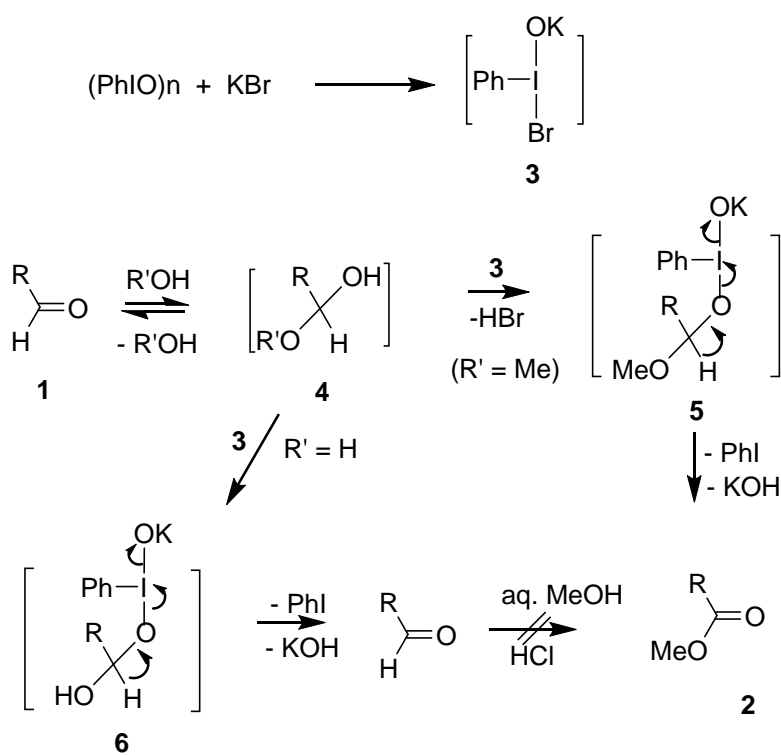
^c Yield of the isolated pure product w.r.t. aldehyde **1**.

^d The quantity of the reagents and methanol was doubled.

To study the further scope of this approach, we also carried out oxidation of *p*-chlorobenzaldehyde using two other alcohols, namely ethanol and 2-propanol. It was observed that the use of methanol is critical for the success of this oxidative transformation as in these

other cases we were unable to isolate the corresponding ester in any detectable amount. Of course, iodosobenzene was quantitatively reduced to iodobenzene.

A plausible mechanism of this IOB mediated conversion of **1** to **2**, outlined in **Scheme 2**, is analogous to that suggested by Kita *et al.* for the oxidative conversion of alcohols into esters. Reactive I(III) species **3**, which is generated *in situ* by depolymerization of iodosobenzene with KBr, reacts with hemiacetal **4** ($R' = \text{Me}$) to give O-I(III) intermediate **5**. Subsequent reductive elimination of iodobenzene gives the ester **2**. The alternative possibility – that the carboxylic acid, **7**, formed by the oxidation of aldehyde **1** through **4** ($R' = \text{H}$) and then intermediate **6**, undergoes esterification – is less likely under aqueous conditions. When benzoic acid was used instead of benzaldehyde under identical conditions, no trace of methyl benzoate could be isolated.



Scheme 2

Conclusions

The present study offers a new and convenient method for the conversion of a variety of aldehydes into the corresponding methyl esters. The method has advantages over the existing methods for the following reasons:

(i) The experimental procedure is very simple and conditions are mild.

- (ii) It does not involve expensive and toxic transition metal oxidants.
- (iii) It is environmentally acceptable.
- (iv) The iodobenzene produced quantitatively by the reductive elimination can be recycled to IOB.
- (v) Examples covered in the present work illustrate its utility for the synthesis of three aliphatic, four aromatic and three heteroaromatic esters; synthetic application to other heteroaromatic and complex esters are to be investigated.

Experimental Section

General. Melting points were taken in open capillaries in a sulfuric acid bath and are uncorrected. ^1H NMR spectra were recorded on a Bruker 400-MHz instrument using TMS as an internal standard. The methyl esters **2** were confirmed by comparison with literature melting points and ^1H NMR data. Column chromatography was performed using 63-200 mesh silica gel (Merck).

Iodosobenzene was prepared according to the literature procedure^{21,22,23} by hydrolysis of commercially available (diacetoxyiodo)benzene.

General procedure for 2a-2j. To a magnetically stirred solution of aldehyde (1 mmol), and potassium bromide (0.5 mmol) in MeOH (10 mL) was added dropwise 0.5 N HCl (2 mL) followed by iodosobenzene (1.5 mmol; 330 mg) and the solution stirred. Progress of the reaction was monitored by TLC. After completion of reaction, the mixture was diluted with H₂O followed by extraction using CH₂Cl₂ (2×10 mL). The combined organic phase was dried over anhydrous Na₂SO₄ and solvent was removed by distillation to give crude product, which was purified by column chromatography (petroleum ether and EtOAc). Purity of the liquid products was checked by tlc and satisfactory elemental analysis (C, H). All the solid products were finally purified by recrystallization by using minimum amount of methanol. For the products **2e**, **2f** and **2g**, the hot methanolic solution was slowly cooled to room temperature and then left in refrigerator for few hours.

Methyl hexanoate (2a). IR (ν_{max} , neat): 1723 cm⁻¹ (C=O), ^1H NMR (CDCl₃, δ): 3.66 (s, 3H), 2.30 (t, *J* 8 Hz, 2H), 1.66 (m, 2H), 1.33 (m, 2H), 0.89 (m, 5H).

Methyl octanoate (2b). IR (ν_{max} , neat): 1722 cm⁻¹ (C=O), ^1H NMR (CDCl₃, δ): 3.64 (s, 3H), 2.28 (t, *J* 7 Hz, 2H), 1.60 (m, 2H), 1.27 (m, 8H), 0.87 (t, 3H).

Methyl nonanoate (2c). IR (ν_{max} , neat): 1724 cm⁻¹ (C=O), ^1H NMR (CDCl₃, δ): 3.82 (s, 3H), 2.1 (t, *J* 6 Hz, 2H), 1.42 (m, 2H), 1.10-1.22 (m, 10H), 0.85 (t, 3H).

Methyl benzoate (2d). IR (ν_{max} , neat): 1728 cm⁻¹ (C=O), ^1H NMR (CDCl₃, δ): 3.90 (s, 3H, OCH₃), 7.32-7.49 (m, 3H, Ar-H), 7.99-8.02 (d, 2H, Ar-H).

Methyl 4-chlorobenzoate (2e). Mp 42-44 °C (lit. mp 44 °C)²⁷, IR (ν_{\max} , KBr): 1715 cm⁻¹ (C=O), ¹H NMR (CDCl₃, δ): 3.89 (s, 3H, OCH₃), 7.41-7.59 (d, 2H, *J* 8.3 Hz, Ar-H), 7.89-8.02 (d, 2H, *J* 8.3 Hz, Ar-H).

Methyl 4-methylbenzoate (2f). Mp 34 °C (lit. mp 33-36 °C)²⁷, IR (ν_{\max} , neat): 1728 cm⁻¹ (C=O), ¹H NMR (CDCl₃, δ): 2.41 (s, 3H, CH₃), 3.92 (s, 3H, OCH₃), 7.32-7.49 (d, 2H, *J* 8.0 Hz, Ar-H), 7.99-8.02 (d, 2H, *J* 8.0 Hz, Ar-H).

Methyl 4-methoxybenzoate (2g). Mp 49 °C (lit. mp 49-51 °C)²⁷, IR (ν_{\max} , neat): 1730 cm⁻¹ (C=O), ¹H NMR (CDCl₃, δ): 3.89 (s, 3H, OCH₃), 3.92 (s, 3H, OCH₃), 7.00-7.15 (d, 2H, *J* 8.2 Hz, Ar-H), 7.29-7.40 (d, 2H, *J* 8.2 Hz, Ar-H).

Methyl 4-nitrobenzoate (2h). Mp 94-96 °C (lit. mp 96 °C)²⁷, IR (ν_{\max} , KBr): 1705 cm⁻¹ (C=O), ¹H NMR (CDCl₃, δ): 3.99 (s, 3H, OCH₃), 7.61-7.82 (d, 2H, *J* 8.0 Hz, Ar-H), 8.01-8.02 (d, 2H, *J* 8.0 Hz, Ar-H).

Methyl 2-furancarboxylate (2i). IR (ν_{\max} , neat): 1770 cm⁻¹ (C=O), ¹H NMR (CDCl₃, δ): 3.99 (s, 3H, OCH₃), 7.15 (d, 1H, *J* 4.55 Hz), 7.88 (d, 1H, *J* 3.70 Hz) 6.68 (m, 1H, *J* 1.30 Hz).

Methyl 2-thiophenecarboxylate (2j). IR (ν_{\max} , neat): 1768 cm⁻¹ (C=O), ¹H NMR (CDCl₃, δ): 3.93 (s, 3H, OCH₃), 7.80 (d, 1H, *J* 3.70 Hz), 7.10 (m, 1H, *J* 1.30 Hz) 7.55 (d, 1H, *J* 5.00 Hz).

Dimethyl 2,5-thiophenedicarboxylate (2k). Mp 83-84 °C (lit. mp 82-83 °C)²⁸, IR (ν_{\max} , neat): 1766 cm⁻¹ (C=O), ¹H NMR (CDCl₃, δ): 3.93 (s, 6H, OCH₃), 7.75 (s, 2H). This was prepared according to general procedure, but the quantity of the reagents and solvent MeOH was doubled and the reaction mixture was allowed to stir at rt for 4 h.

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