An efficient and mild direct oxidative methyl esterification of aromatic aldehydes using NaBr and diacetoxyiodobenzene

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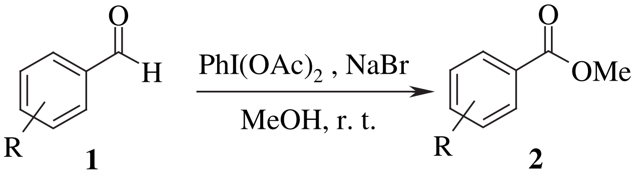
Diacetoxyiodobenzene combined with NaBr was found to be an efficient, mild and practical reagent for the oxidative methyl esterification of aldehydes.

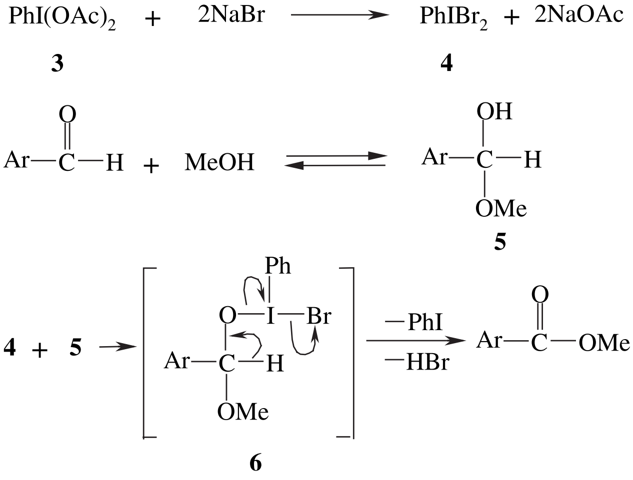
Keywords: aromatic aldehydes, esterification, hemiacetal, hypervalent iodine

The direct oxidative transformation of aldehydes to esters is an extremely useful and selective functional group interconversion in organic synthesis.[1] A two-step reaction sequence involving the oxidation of hemiacetals,[2] acetals[3] or cyanohydrins[4] can bring about this conversion. Several one-pot conversions using environmentally unacceptable complexes of different heavy metal oxidants such as rhenium,[5] rhodium,[6] ruthenium,[7] MnO_2,[8] pyridinium dichromate[9] and the highly expensive silver[10] have been reported. The efficacy of this strategy has been improved by several groups to include hydrogen peroxide[11] as the principal oxidant coupled with a catalytic quantity of V_2O_5[12] and titanosilicates.[13] The other oxidative esterification protocol uses *N*-halosuccinimide,[14] chlorites,[15] ammonium persulfate,[8] and photochemical[16] as well as electrochemical[18] reaction conditions. However, most of the methods are associated with some drawbacks, which include the use of hazardous and expensive or commercially non-available reagents, long reaction times, low yields due to occurrence of several side reactions, drastic reaction conditions and tedious work up procedure. Therefore, it is worthwhile to look for an efficient, mild and practical method for the one-pot conversion of aldehydes into the corresponding esters.

The chemistry of hypervalent iodine reagents in organic synthesis is a most fascinating and fertile field for interesting functional group manipulations.[18] Diacetoxyiodobenzene (DIB), is a popular hypervalent iodine reagent, which is easy to handle, non-toxic, commercially available and is similar in reactivity to heavy metal reagents.[19] The oxidising capacity of DIB has recently been remarkably modified by adding bromide ions as a co-catalyst in several useful reactions such as the clean oxidation of alcohols in an aqueous medium,[20] rapid bromination of activated aromatics and bromolactonisation or dibromination of olefins.[21] In continuation of our interest in hypervalent iodine reagents,[22] we wish to report herein the use of DIB combined with NaBr in the facile and direct oxidative methyl esterification of aromatic aldehydes (Scheme 1).



Scheme 1



Scheme 2

To study this process, we have examined the model reaction of *m*-nitrobenzaldehyde (1 mmol) with NaBr (2 mmol) in methanol (15 ml). When DIB (1.1 mmol) was added to the above stirred reaction mixture at room temperature, the solution immediately turns yellow. After completion of reaction within 2 h, the corresponding methyl *m*-nitrobenzoate, m.p. 78–80 °C (lit.,[23] 78–80 °C) was obtained in 94 % yield.

Mechanistically, the *in situ* generation of $PhIBr_2$ **4** by the ligand exchange reaction between $PhI(OAc)_2$ **3** and NaBr is expected (Scheme 2). The actual oxidation reaction may proceed through the initial reaction of the fairly electrophilic $PhIBr_2$ **4** with the nucleophilic hydroxy group of the hemiacetal[14b] **5** to give the intermediate **6**. The overwhelming tendency of intermediate **6** for the reductive elimination of iodobenzene[24] will promote the concomitant oxidation of hemiacetals to esters. Another mechanistic possibility is the oxidation of hemiacetal **5** to an ester induced by the molecular bromine[5] generated *in situ* by the reductive elimination of iodobenzene from $PhIBr_2$ **4**.[21] To gain some insight into the mechanism of this reaction, we have attempted the methyl esterification in the absence of NaBr as well as the possible oxidative esterification of benzoic acid with NaBr / DIB in methanol. Note that no methyl ester formation is observed in either case.

The results reported in the Table 1 show that the method is practically simple, with fast reaction times, giving good to excellent yields of the methyl esters of aromatic aldehydes containing electron-releasing and -withdrawing substituents. Thus anisaldehyde (entry 1) underwent a clean oxidative esterification to form methyl *p*-methoxybenzoate in 98 % yield. This is in contrast to the formation of *p*-methoxyphenol from anisaldehyde using the titanosilicates/H_2O_2 combination.[13] Other methoxy benzaldehydes (entries 2–3) also yield corresponding methyl esters in quantitative yield. *p*-Methyl and *p*-bromobenzaldehyde (entries 4–5) also provide corresponding methyl esters in excellent yields. Under similar reaction conditions, benzaldehyde (entry 6) is converted into methylbenzoate in 72% yield. The aromatic aldehydes with

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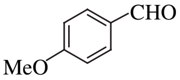
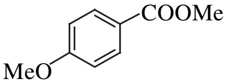
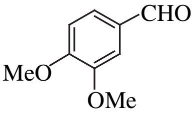
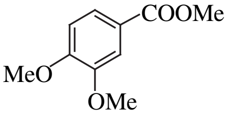
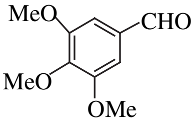
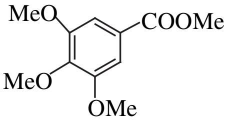
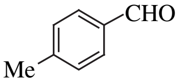
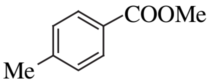
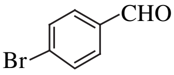
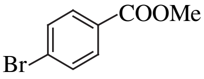
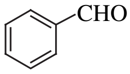
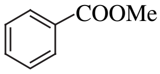
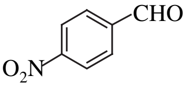
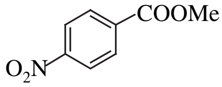
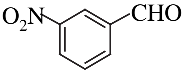
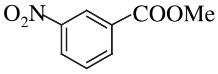
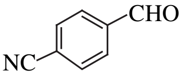
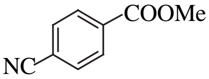
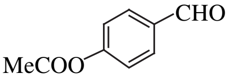
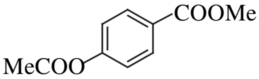
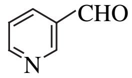
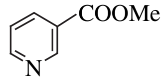
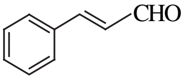
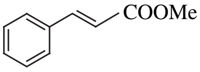
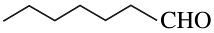
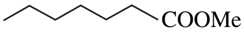
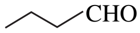
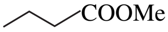
Table 1 Direct oxidative methyl esterification of aldehydes using NaBr and DIB[a]

Entry	Substrate	Product	Yield[b,c] /%	M.p. /°C
1			97	49 (49–51)
2			93	60 (59–62)
3			88	83 (82–84)
4			91	34 (33–36)
5			92	78 (77–81)
6			72	Liquid
7			96	95 (94–96)
8			91	78 (78–80)
9			90	67 (67–68)
10			93	83 (82–84)
11			86	43 (42–43)
12[d]			18	35 (33–36)
12			86	Liquid
13			83	Liquid

[a]All reactions were carried out in methanol solvent for 2 h. stirring at room temperature. [b]Isolated yields after chromatography. [c]Products are characterised by IR, NMR, melting points and comparison with authentic samples. [d]Dibromo derivative in 73 % yield is formed.

electron-withdrawing groups (entries 7—10) and 3-pyridine-carboxyldehyde (entry 11) also underwent clean oxidative methyl esterification in high yields. However, the reaction of cinnmaldehyde (entry 12) with DIB/NaBr in methanol produces a mixture of products consisting of the dibromo derivative in major quantity (73%) and methyl cinnamate in a poor 18 % yield. Finally, the aliphatic aldehydes such as heptanal and butanal (entries 13—14) also yield the corresponding methyl esters in excellent yields.

In summary, an efficient method for the facile conversion of aromatic aldehydes into methyl esters has been developed under mild conditions with high yields using DIB combined with NaBr in methanol. This reagent avoids some of the difficulties associated with the use of heavy metal derivatives, especially in the large scale reactions, such as toxicity, troublesome work up procedures and the need to use an excess of oxidising agent.

General procedure

To a solution of aldehyde (1mmol), NaBr (2 mmol) in methanol (15 ml) was added diacetoxyiodobenzene (1.1 mmol). The reaction mixture immediately turned yellow and was then subjected to stirring for 2 hours at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, water (10 ml) was added and the mixture extracted with CH_2Cl_2 (2 × 10 ml). The combined organic extracts were dried over anhydrous sodium sulfate, concentrated in vacuo and chromatographed to give methyl esters.

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