A Simple Procedure for the Oxidation of Alcohols Using [Bis(acetoxy)iodo]benzene and a Catalytic Amount of Bromide Ions in Ethyl Acetate

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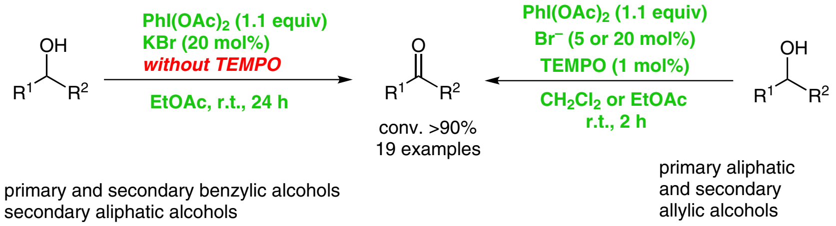

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Abstract Primary and secondary benzylic alcohols and secondary aliphatic alcohols were oxidized to the corresponding aldehydes and ketones by using [bis(acetoxy)iodo]benzene (BAIB) and a catalytic amount of bromide ions, from tetrabutylammonium bromide or KBr, in ethyl acetate. The catalytic role of the bromide ions was also highlighted in the oxidation of primary aliphatic alcohols and secondary allylic alcohols carried out in the presence of 1 mol% TEMPO.

Keywords alcohols, aldehydes, catalysis, ketones, oxidation

Oxidation of alcohols is a process that has interested chemists for a very long time. The usefulness of the reaction is well known and a large number of oxidation methods is now available. Several methods are based on the use of a stoichiometric amount of metal-based oxidants such as Collins reagent, pyridinium dichromate or chlorochromate.[1] Methods involving the use of a catalytic amount of metal-based oxidants are also available, such as tetrapropylammonium perruthenate in the presence of an excess of *N*-methylmorpholine oxide.[2] Recent demand for green oxidation processes has encouraged the development of cleaner and safer oxidation reactions. The use of soluble metal-based oxidants or catalysts can be avoided by using supported metal catalysts.[3] On the other hand, the use of metal-free catalysts for selective oxidations of organic substrates is very appealing, and several organic oxidants can be used, such as activated dimethyl sulfoxide (DMSO)[4] or catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) in the presence of NaOCl.[5] TEMPO can also be used with stoichiometric amounts of inexpensive, safe, and easy to handle oxidants such as [bis(acetoxy)iodo]benzene (BAIB),[6] trichloro isocyanuric acid,[7] Oxone,[8] or iodine.[9] Among them, hypervalent iodine compounds such as BAIB have been used successfully.[10] Pentavalent iodine reagents such as Dess–Martin periodinane[11] and *o*-iodoxybenzoic acid[12] are mild and efficient oxidizing agents that allow carbonyl compounds to be obtained from alcohols with high yields in organic solvents such as CH_2Cl_2, DMSO, and acetone. However, iodine(V) reagents cannot be stored for a long time. In place of iodine(V) reagents, readily available and relatively stable iodine(III) reagents can be used. The group of Kita has described several examples of oxidation of alcohols by using iodine(III) reagents. They reported the use of iodosobenzene (PhIO) with KBr, in water under neutral conditions[13] as well as the use of polymer-supported (diacetoxyiodo)benzene (PSDIB).[14] Under these conditions, acids, ketones, and lactones were obtained. Instead of KBr, the same authors employed $Et_4N^+Br^-$ in water. Under the latter conditions, several secondary alcohols were easily converted into the corresponding ketones; usually, one equivalent of $Et_4N^+Br^-$ was used. These reactions were also carried out with a recyclable adamantane-type hypervalent iodine(III) reagent in the presence of 0.5 equivalent $Et_4N^+Br^-$.[15] Very recently, $Bu_4N^+Br^-$ was used in 5 mol% in the presence of *t*-butylhydroperoxide (2 equiv) for the oxidation of primary and secondary benzylic alcohols, but reactions were carried out in the carcinogen benzene.[16] Iodosobenzene was also used in the presence of Ph_4PBr in CH_2Cl_2 for the oxidation of benzylic and secondary aliphatic alcohols.[17] Another approach is the use of ion-supported BAIB derivatives in ionic liquid.[18] The BAIB/KBr/chiral Mn(III)Salen system was used in the oxidative kinetic resolution of racemic secondary alcohols.[19] Iodine(III) reagents were also used in the presence of variable amounts of TEMPO.[20–23]

Recently, we described the oxidation of alcohols by using new imidazolium bromide-based TEMPO catalysts.[24] In particular, we observed a synergic effect when fullerene-based catalyst **1** was used (Figure 1).[25] These reactions were carried out with $PhI(OAc)_2$ (1.1 equiv). To develop a 'release

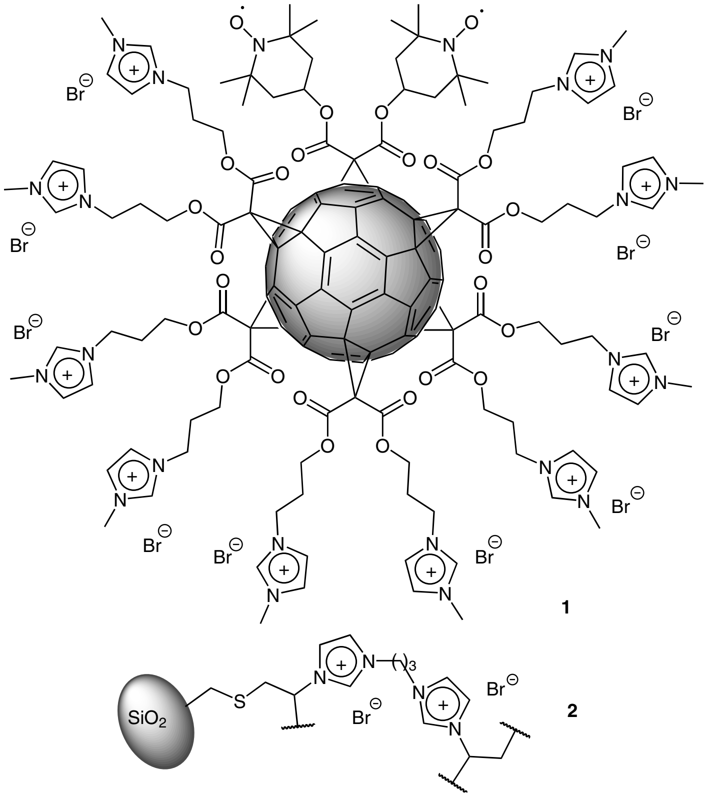


Figure 1 Structure of catalysts **1** and **2**

and catch'[26] system for such oxidation reaction, catalyst **1** was adsorbed on imidazolium bromide-modified silica gel **2** (Figure 1); by using this system, we observed a catalytic effect of the support (Table 1, entry 1). We then investigated the use of $PhI(OAc)_2$ (1.1 equiv) in the presence of a catalytic amount of bromide ions as oxidizing system *without* the use of TEMPO. Although similar studies have been described (see above), in such papers, reactions have been carried out in water giving only ketones, whereas primary alcohols gave carboxylic acids. Although the use of water is environmentally acceptable, the final product was extracted from the aqueous solution by using an organic solvent. We then decided to perform the present study in organic solvent. As sources of bromide ions, in place of the supported imidazolium bromide salt we used the soluble tetrabutylammonium bromide (TBAB).

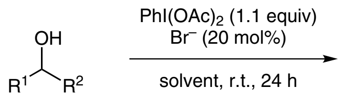
Reactions were carried out at room temperature for 24 h, although the reaction times were not optimized.[27] The oxidation reactions were first carried out by using 1-phenylethanol in CH_2Cl_2 (Table 1). The use of TBAB as catalyst (20 mol%) gave the ketone in almost quantitative conversion (95%, entry 2). The amount of TBAB could be lowered (5 mol%) and reaction time could also be shortened (6 h) while still giving good conversion (entry 3). Benzyl alcohol gave benzaldehyde in high conversion (92%, entry 4), thus showing that it is possible to obtain aldehydes without oxidation to carboxylic acids. However, because the use of a chlorinated solvent such as dichloromethane is not environmentally friendly, we decided to employ a much greener solvent such as ethyl acetate. Use of this solvent has been described for the oxidation of alcohols in the presence of aqueous NaOCl and TBAB[28–29] and in the presence of iodine(III) reagent/TEMPO/pyridine.[30]

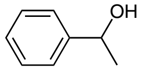
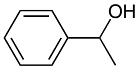
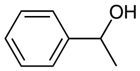
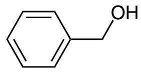
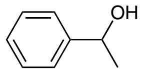
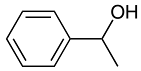
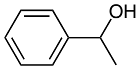
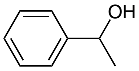
Oxidation of 1-phenylethanol in ethyl acetate, in the presence of TBAB, gave the corresponding ketone with quantitative conversion, even after a shorter reaction time (entries 5 and 6). Reactions carried out by using only $PhI(OAc)_2$ gave low conversions (entries 7 and 8).

By using TBAB and ethyl acetate as solvent, we carried out the oxidation of a set of alcohols (Table 2). Diphenylmethanol was easily converted into benzophenone (Table 2, entry 1). Benzyl alcohol was converted into the corresponding aldehyde with high conversion (entry 2). Reactions with other benzylic alcohols were carried out on a 2 mmol scale.

4-Chlorobenzyl alcohol gave the corresponding aldehyde in 67% isolated yield (Table 2, entry 3), whereas anisaldehyde was isolated in 95% yield (entry 4). The same reaction carried out using 4-nitrobenzyl alcohol gave the corresponding aldehyde in only 30% yield (entry 5); in this case, ester **3** (Figure 2) was also isolated (40%). 2-Naphthalenemethanol gave the corresponding aldehyde with quantita-

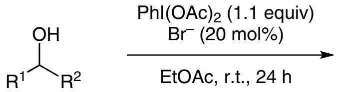
Table 1 Catalyst and Solvent Screening for Oxidation of Alcohols[a]

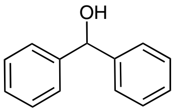
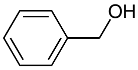
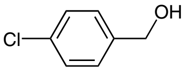
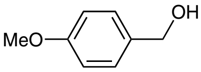
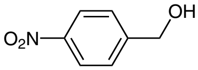
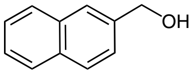
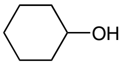
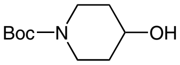
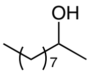
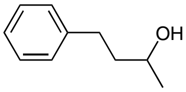


Entry	Catalyst	Alcohol	Solvent	Conv. (%)[b]
1[c]	**2**		CH_2Cl_2	34
2	TBAB		CH_2Cl_2	95
3[d]	TBAB		CH_2Cl_2	88
4	TBAB		CH_2Cl_2	92
5	TBAB		EtOAc	>95
6[d]	TBAB		EtOAc	>95
7	–		CH_2Cl_2	16
8	–		EtOAc	25

[a] Reaction conditions: alcohol (1 mmol), BAIB (1.1 mmol), solvent (1.5 mL), catalyst (0.2 mmol), 24 h, r.t.
[b] Determined by ^1H NMR spectroscopic analysis.
[c] Beejapur et al.[25]
[d] TBAB (5 mol%), reaction time 6 h.

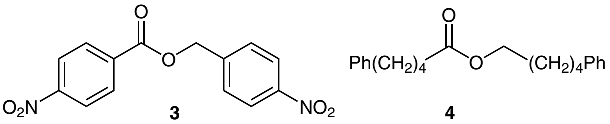
Table 2 Oxidation of Alcohols[a]



Entry	Catalyst	Alcohol	Conv. (%)[b]
1	TBAB		>95
2	TBAB		91
3[c]	TBAB		67[d]
4[c]	TBAB		95[d]
5[c]	TBAB		70[e]
6	TBAB		>95
7	TBAB		>95
8	TBAB		45
9	TBAB		93
10	TBAB		89

[a] Reaction conditions: alcohol (1 mmol), BAIB (1.1 mmol), solvent (1.5 mL), catalyst (0.2 mmol), 24 h, r.t..
[b] Determined by ^1H NMR spectroscopic analysis.
[c] Reaction conducted on 2 mmol scale.
[d] Isolated yield.
[e] Yield of aldehyde: 30%; yield of ester **3**: 40%.

tive conversion (entry 6). Secondary aliphatic alcohols were converted into the corresponding ketones in high conversions, except for *N*-Boc-4-hydroxypiperidine, which gave a moderate conversion (entries 7–10).



3 **4**

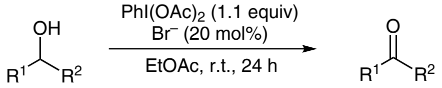
Figure 2 Esters **3** and **4**

Since the insoluble imidazolium salt **2** catalysed the oxidation reaction, although not with high yield (Table 1, entry 1), we reasoned that there may be no need to use soluble TBAB as source of bromide ions; we therefore used the inorganic salts NaBr and KBr (Table 3). An insoluble source of bromide ions is desirable because its use simplifies the purification of the final carbonyl compounds. Through the inclusion of 20 mol% NaBr or KBr, 1-phenylethanol was quantitatively converted (entries 1 and 2), and the use of just 5 mol% NaBr also gave high conversion (entry 3).

By using the less expensive KBr (20 mol%) we then oxidized a set of alcohols. 4-Methoxybenzyl alcohol gave, as major product, the corresponding aldehyde in 60% yield. Other benzylic and secondary aliphatic alcohol gave excellent conversions (entries 5–14).

Under these conditions, *N*-Boc-4-hydroxypiperidine gave a higher conversion (compare Table 3, entry 12 vs. Table 2, entry 8). 4-Phenyl-butan-2-ol was oxidized on a 2 mmol scale to give the corresponding ketone in 84% yield after 24 h. Reaction with a primary aliphatic alcohol (5-phenyl-pentan-1-ol) was unsatisfactory, giving the corresponding ester **4** in 60% yield as the major product (Figure 2).

Table 3 Oxidation of Alcohols in the Presence of NaBr or KBr[a]



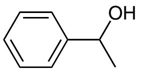
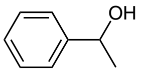
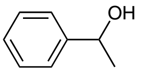
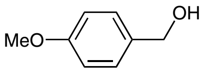
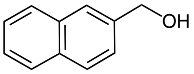
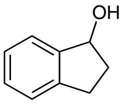
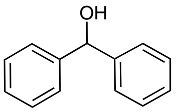
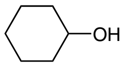
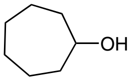
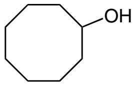
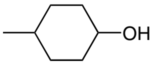
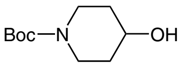
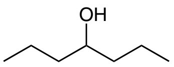
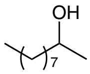
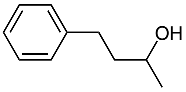
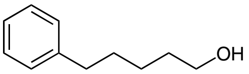
Entry	Catalyst	Alcohol	Conv. (%)[b]
1	NaBr		>95
2	KBr		>95
3[c]	NaBr		90
4[d]	KBr		60[e]
5	KBr		>95
6	KBr		>95
7	KBr		>95
8	KBr		>95
9	KBr		>95
10	KBr		>95
11	KBr		>95
12	KBr		83
13	KBr		>95

Table 3 (continued)

Entry	Catalyst	Alcohol	Conv. (%)[b]
14	KBr		>95
15[f]	KBr		84[e]
16[f]	KBr		60[g]

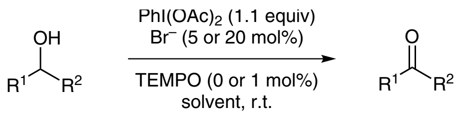
[a] Reaction conditions: alcohol (1 mmol), BAIB (1.1 mmol), solvent (1.5 mL), catalyst (0.2 mmol), 24 h, r.t..
[b] Determined by ^{1}H NMR spectroscopic analysis.
[c] Performed with 5 mol% NaBr.
[d] Reaction on 2 mmol scale, reaction time 5 h.
[e] Isolated yield.
[f] Reaction conducted on 2 mmol scale, reaction time 24 h.
[g] Yield of ester **4**.

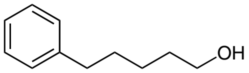
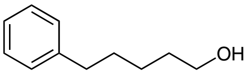
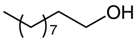
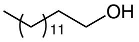
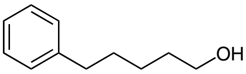
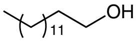
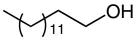
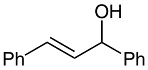
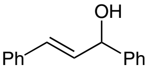
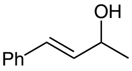
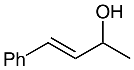
To obtain high yields of aliphatic aldehydes, the reaction was carried out in the presence of TBAB (5 mol%) and a catalytic amount of TEMPO (1 mol%). 5-Phenylpentan-1-ol was oxidized in high conversion (Table 4, entry 1). The catalytic role of bromide ions was evident when the reaction was carried out without TBAB. Conversion was about 70% and reaction was not clean (entry 2). 1-Decanol and 1-tetradecanol were also oxidized in the presence of TBAB and TEMPO (5 and 1 mol%; Table 4, entries 3 and 4), and high conversions were observed after 2 h. The latter reactions were carried out in CH_2Cl_2; however, oxidation in ethyl acetate gave also very high conversion. Indeed, conversion of 5-phenylpentan-1-ol was 95% (entry 5). The role of the catalytic amount of bromide ions was confirmed by carrying out the oxidation of a primary aliphatic alcohol (1-tetradecanol) and two allylic secondary alcohols (*trans*-1,3-diphenylprop-2-en-1-ol and *trans*-4-phenylbut-3-en-2-ol) in ethyl acetate (entries 6–11). In each case, higher conversion was achieved when the reaction was performed in the presence of KBr.

We have also checked the selectivity of this method in the case of benzylic/aliphatic alcohols. Oxidation of an equimolar mixture of 1-indanol/1-decanol in the presence of BAIB and KBr in ethyl acetate gave an excellent selectivity (Scheme 1), whereas a lower selectivity was observed in the case of 1-indanol/2-decanol (Scheme 1).

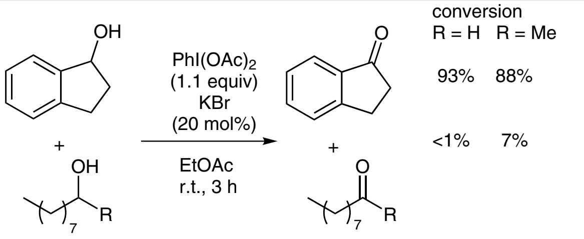
The mechanism of promotion by bromide ions in the presence of BAIB can be explained by the formation of bis(acyloxy)bromate(I) anions,[21] which, in turn, release acetyl hypobromite (AcOBr)[31] and potassium acetate (Scheme 2, paths *a* and *b*). Oxidation mediated by AcOBr (path *c*) gives the carbonyl compound, whereas proton exchange between acetate and HBr gives the starting bromide salt (path

Table 4 Oxidation of Alcohols in the Presence of TEMPO/Bromide Ions or TEMPO[a]



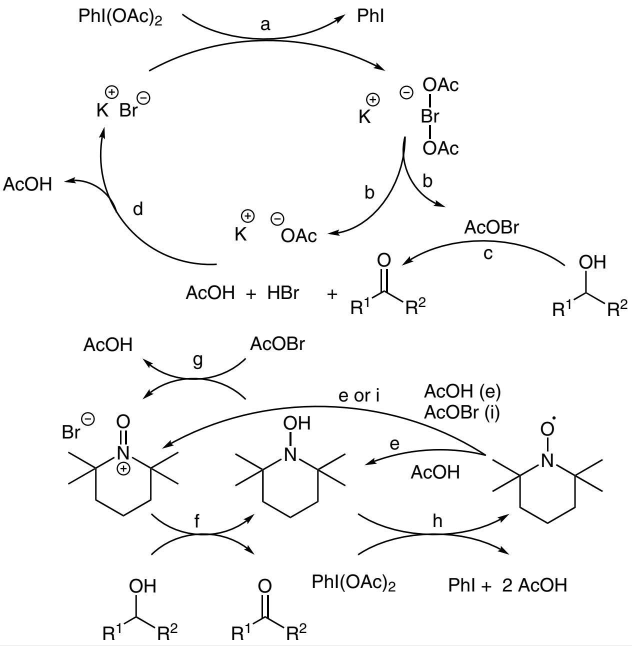
Entry	Conditions	Alcohol	Time (min)	Conv. (%)[b]
1	TBAB, TEMPO CH_2Cl_2		120	95
2	TEMPO CH_2Cl_2		120	70
3	TBAB, TEMPO CH_2Cl_2		120	92
4	TBAB, TEMPO CH_2Cl_2		120	90
5	TBAB, TEMPO EtOAc		120	95
6	KBr, TEMPO EtOAc		90	>99
7	TEMPO EtOAc		90	86
8	KBr, TEMPO EtOAc		90	>99
9	TEMPO EtOAc		90	81
10	KBr, TEMPO EtOAc		265	90
11	TEMPO EtOAc		265	81

[a] Reaction conditions: alcohol (1 mmol), BAIB (1.1 mmol), TBAB (5 mol%) or KBr (20 mmol%), TEMPO (1 mol%), solvent (1.5 mL).
[b] Determined by ^1H NMR spectroscopic analysis.



Scheme 1 Oxidation of an equimolar mixture of 1-indanol/1-decanol or 1-indanol/2-decanol in the presence of BAIB and KBr

d). Oxidation of primary aliphatic alcohols with BAIB, TEMPO and bromide can be explained with the additional paths *e*–*i*.



Scheme 2 Oxidation of alcohols in the presence of BAIB and Br^- (paths *a*–*d*) and BAIB, TEMPO and Br^- (paths *e*–*i*)

In this case, in addition to paths *a*–*d*, other pathways can take place. First, TEMPO undergoes a dismutation in the presence of AcOH (path *e*); [32] oxoammonium salt oxidizes the alcohol to the carbonyl compound (path *f*) giving TEMPOH. TEMPOH can be reconverted into oxoammonium salt by oxidation with AcOBr (path *g*). TEMPOH can also be reconverted into TEMPO by BAIB (path *h*). In addition, AcOBr can oxidize TEMPO to oxoammonium salt (path *i*).[21] The crucial role played by bromide ions in the oxidation of primary aliphatic alcohol with the system BAIB, TEMPO and Br^- could be ascribed to paths *g* and *i*, which increases the efficiency of the entire catalytic system. Isolation of esters **3** and **4** (Figure 2) can be ascribed to the slow formation of the aldehyde and its transformation into the corresponding hemiacetal and subsequent oxidation to ester.[33]

In conclusion, we have demonstrated that primary and secondary benzylic alcohols and secondary aliphatic alcohols can be oxidized to the corresponding carbonyl compounds by simple treatment with $PhI(OAc)_2$ and a catalytic amount of TBAB or KBr in ethyl acetate at room temperature. The advantages of this approach are: (i) ready availability of the oxidizing molecules and simple procedure; (ii) use of a green solvent; (iii) no use of water that causes oxidation to carboxylic acids and that requires the use of organic solvent for extraction of the carbonyl compounds making the entire process less environmental benign; (iv) high selectivity of benzylic vs. primary and secondary aliphatic alcohols. The addition of a catalytic amount of TEMPO allowed the oxidation of primary aliphatic alcohols as well as secondary allylic alcohols. The presence of a catalytic amount of bromide ions is useful to increase the conversion, probably due to oxidation of TEMPOH to the oxoammonium salt mediated by acetyl hypobromite or bis(acyloxy)bromate(I) anion. The use of unsupported bis(acyloxy)bromate(I) anion allows the use of a minor amount of BAIB with respect to the supported system[21] and avoids, in many cases, the use of TEMPO.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380196.

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(27) **Oxidation Procedure**: Alcohol (1 mmol) was added to a mixture of BAIB (1.1 mmol) and bromide anions (0.2 mmol) in EtOAc (1.5 mL), and the mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the crude product was checked by ^{1}H NMR spectroscopy. In case of *p*-nitrobenzyl alcohol, anisole, and *p*-chlorobenzyl alcohol oxidations, the residue was purified by chromatography [PE to separate iodobenzene and PE–EtOAc (10:1) to separate the corresponding aldehyde].
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