4,4′-Bis(dichloroiodo)biphenyl and 3-(Dichloroiodo)benzoic Acid: New Recyclable Hypervalent Iodine Reagents for Vicinal Halomethoxylation of Unsaturated Compounds

Mehman S. Yusubov,*a,b Larisa A. Drygunova,b Viktor V. Zhdankina

a The Siberian Medical State University, 2 Moskovsky trakt, 634050 Tomsk, Russia
b Tomsk Polytechnic University, 30 Lenin st., 634050 Tomsk, Russia
c Department of Chemistry, University of Minnesota Duluth, Duluth, MN 55812, USA
E-mail: yusubov@mail.ru

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Dedicated to Professor N. S. Zefirov on his 70th anniversary

Abstract: 4,4′-Bis(dichloroiodo)biphenyl and 3-(dichloroiodo)benzoic acid are convenient recyclable hypervalent iodine reagents for vicinal chloromethoxylation or iodomethoxylation of unsaturated compounds. The reactivity of these reagents in the reaction of vicinal halomethoxylation is generally similar to dichloroiodobenzene, 1 and the advantage of their use is that the reduced forms of these reagents can be easily separated from the reaction mixture and reused for the regeneration of the reagents.

Key words: hypervalent iodine, halogens, electrophilic additions, oxidations, alkenes

Hypervalent iodine reagents have emerged as reagents of choice for various synthetically useful oxidative transformations.1 The commonly used reagents, such as dichloroiodobenzene, iodosylbenzene, (diacetoxy)iodobenzene, and [hydroxy(tosyloxy)iodo]benzene, are based on the oxidized forms of iodobenzene. The reactions of these reagents with organic substrates lead to iodobenzene as the byproduct, which is difficult to recover and reuse because of the high volatility and solubility in organic solvents. Several research groups have tried to improve the iodobenzene-based hypervalent iodine reagents by developing their polymer-supported analogs.2,3 In particular, it has been demonstrated that poly(diacetoxyiodo)styrene shows the reactivities similar to (diacetoxy)iodobenzene and can be utilized as the environmentally benign replacement for hypervalent iodine reagents.1 Despite the utility of the polymer-supported reagents, they still have several drawbacks. These reagents require a multistep preparation, they have lower reactivity compared to the corresponding monomeric analogs, and, moreover, the repeated use of these polymers leads to significant degradation due to the benzylic oxidation of the polystyrene chain. We wish to report the preparation and reactivity of new recyclable nonpolymeric hypervalent iodine chlorides 2 and 4. Reagents 2 and 4 can be conveniently prepared by simple chlorination of the commercially available iodides 1 and 3 (Scheme 1), their reactivity is similar to the practically useful dichloroiodobenzene,1 and the products of their reactions with organic substrates can be easily separated from reaction mixtures in almost quantitative yields and reused for the regeneration of reagents 2 and 4.

4,4′-Bis(dichloroiodo)biphenyl (2) was prepared by saturating a solution of 4,4′-diiodobiphenyl (1) in CHCl3 with gaseous chlorine for one hour at room temperature under stirring. Product 2 was isolated in high yield as a yellow, stable and non-explosive microcrystalline solid; it can be stored for several weeks in a refrigerator in dark. Chlorine content in 2 was analyzed by iodometric titration.

Scheme 1

Compound 2 is a convenient chlorinating reagent and its reduced form, 4,4′-diiodobiphenyl (1), is practically insoluble at room temperature in organic solvents that are commonly used as reaction media (hydrocarbons, alcohols, carbonic acids etc.). The low solubility allows convenient separation of 4,4′-diiodobiphenyl from reaction products by simple filtration and reuse for the regeneration of reagent 2. At the same time, 4,4′-diiodobiphenyl (1) has excellent solubility in CHCl3, which is important for the preparation of 2 by chlorination of 1 under homogeneous conditions. Reagent 2 has several obvious advantages over the polymer-supported hypervalent iodine reagents: (i) it is significantly cheaper and easy to prepare from a readily available precursor, (ii) reagent 2 has high recyclability without degradation loss, (iii) it has high loading efficiency, and (iv) analytical control of the quality of the reagent can be conveniently performed by iodometric titration.

Synthetic utility of reagent 2 was investigated in the reactions of chloro- and iodomethoxylation of unsaturated compounds.4,5 In particular, in the reaction of 2 with styrene derivatives 5a–c in MeOH the products of electro-
philic chloromethoxylation 6a–c were isolated in 60–70% yield. In addition, the reaction mixture contained small amount (2–7%) of vicinal dichlorides. A similar reaction of reagent 2 with alkenes in the presence of iodine in MeOH led to the products of iodomethoxylation 7a,b,d,e in 60–90% yields, but not the chloromethoxylation products (Scheme 2).

Scheme 2

Under similar conditions, the reaction of reagent 2 with (1S)-(+)-3-carene (5f) in the presence of iodine afforded product 7f that was isolated by column chromatography in 22% yield (Scheme 3).

Scheme 3

Reaction of phenylacetylene 8 with 2 in MeOH produced 2,2-dichloro-1,1-dimethoxy-1-phenylethane (9) in 61% yield (Scheme 4).

Scheme 4

Comparison of these results with the previously reported reactions of dichloroiodobenzene with alkenes under similar conditions leads to a conclusion that the reactivity of reagent 2 in the reactions of vicinal halomethoxylation of unsaturated compounds is generally similar to dichloroiodobenzene. However, the reaction of 2 with styrene 5a the presence of iodine in MeOH was different from the reaction of dichloroiodobenzene. In this case, in addition to the iodomethoxylation product, a small amount (2%) of 1-(1-chloro-2-iodoethyl)benzene was obtained as a product of vicinal iodochlorination. Likewise, in the reaction of 4-phenyl-1-butene (5g), besides the anticipated iodomethoxylation product, iodochlorination products were obtained in significant amounts (Scheme 5). Two fractions were isolated by column chromatography of the reaction mixture: the first one was a non-separable mixture of two regioisomers 7g and 10 of iodomethoxylation reaction in the ratio of 2:1 with total yield of 43%, and the second fraction was a non-separable mixture of iodochlorination products 11 and 12 (1:1 ratio) with total yield of 29%.

Scheme 5

We assume that compounds 10–12 are formed via a mechanism involving the intermediate formation of alkylaryl-iodonium ion, similarly to the previously reported reactions of KICl2 and KICl4 with alkenes, resulting in the formation of the regioisomeric vicinal iodochloroalkanes.

Table 1 Halomethoxylation of Unsaturated Compounds with 4,4'-Bis(dichloroiodo)biphenyl (2) and 3-(Dichloroiodo)benzoic Acid (4)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent/Conditionsa</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>I2/MeOH</td>
<td>0.25</td>
<td>7a</td>
<td>65</td>
</tr>
<tr>
<td>5b</td>
<td>I2/MeOH</td>
<td>0.25</td>
<td>7b</td>
<td>85</td>
</tr>
<tr>
<td>5c</td>
<td>I2/MeOH</td>
<td>0.25</td>
<td>7c</td>
<td>82</td>
</tr>
<tr>
<td>5d</td>
<td>I2/MeOH</td>
<td>0.25</td>
<td>7d</td>
<td>85</td>
</tr>
<tr>
<td>5e</td>
<td>I2/MeOH</td>
<td>0.25</td>
<td>7e</td>
<td>82</td>
</tr>
<tr>
<td>5f</td>
<td>I2/MeOH</td>
<td>0.25</td>
<td>7f</td>
<td>22</td>
</tr>
<tr>
<td>5g</td>
<td>I2/MeOH</td>
<td>0.25</td>
<td>7g + 10</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 + 12</td>
</tr>
<tr>
<td>6a</td>
<td>2/MeOH</td>
<td></td>
<td>6a</td>
<td>62</td>
</tr>
<tr>
<td>6b</td>
<td>2/MeOH</td>
<td></td>
<td>6b</td>
<td>66</td>
</tr>
<tr>
<td>6c</td>
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<td>57</td>
</tr>
<tr>
<td>6d</td>
<td>2/MeOH</td>
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</tr>
<tr>
<td>6e</td>
<td>2/MeOH</td>
<td></td>
<td>6e</td>
<td>82</td>
</tr>
<tr>
<td>6f</td>
<td>2/MeOH</td>
<td></td>
<td>6f</td>
<td>22</td>
</tr>
<tr>
<td>6g</td>
<td>2/MeOH</td>
<td></td>
<td>6g</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7g + 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 + 12</td>
</tr>
</tbody>
</table>

a All reactions were carried out at r.t.

b Yields of products isolated after column chromatography.
The second chlorinating reagent, 3-(dichloroiodo)benzoic acid (4), can be conveniently prepared by the chlorination of the commercially available 3-iodobenzoic acid (3) (Scheme 1). Reagent 4 is specifically attractive due to the fact that its reduced form 3 can also be easily separated from the products of chlorination. It is possible due to the high solubility of 3-iodobenzoic acid (3) and its salts in aqueous solutions. Therefore the recovery of 3 from the reaction mixture can be successfully performed by the treatment with 5% aqueous solution of sodium bicarbonate.

We investigated the reactivity of 4 in iodomethoxilation reaction of alkenes. The expected products 7a,b,d were isolated in good yields from the reactions of 4 with alkenes 5 in MeOH in the presence of iodine (Scheme 6). It should be noted that the reaction of 4-phenyl-1-butene (5g) with 4 and iodine in MeOH afforded methoxyiodides 7g and 10, as well as the regioisomeric iodochlorination products 11 and 12, in the same ratios, as in the reaction of reagent 2.

In conclusion, 4,4′-bis(dichloroiodo)biphenyl (2) and 3-(dichloroiodo)benzoic acid (4) are convenient recyclable hypervalent iodine reagents for vicinal halomethylation of unsaturated compounds. These reagents combine the properties of the common polyvalent iodine compounds and their polymer-supported analogs. The reactivity of these reagents in the reaction of vicinal halomethylation of unsaturated compounds is generally similar to dichloroiodobenzene and the advantage of their use is that the reduced forms of these reagents can be easily separated from the products of halogenation of organic substrates.

All melting points were determined using a Boetius melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Vector-22 spectrophotometer. 1H NMR and 13C NMR spectra were recorded on a Bruker AM-300 NMR spectrometer (300.13 MHz and 75.47 MHz) and DRX 500 (500 MHz and 125 MHz) using TMS as internal standard. Chemical shifts are reported in ppm. GC–MS spectra were obtained using gas chromatograph equipped with quadrupole mass-spectrometer Hewlett Packard 5890/II as detector (EI, 70 eV). High resolution EI mass spectra (EI, 70 eV) were recorded on Finnigan MAT 8200 mass spectrometer. Microanalyses were carried out using 1106 Carlo Erba CHNS-O analyzer. Flash column chromatography was performed on silica gel (L40/100 μm; purchased from Chempol) or aluminum oxide (neutral, Brockmann II; purchased from Roanal). TLC was performed on silica gel plates Sorbfil (made in Russia).

1-Iodo-2-methoxy-4-phenylbutane (7g)

1H NMR (300 MHz, CDCl3): δ = 1.87 (m, 2 H, 3-CH2), 2.63 (m, 2 H, 4-CH2), 2.95 (m, 1 H, 2-CH), 3.21 (m, 2 H, 1-CH2), 3.32 (s, 3 H, OCH3), 7.12–7.25 (m, 5 H arom.).

13C NMR (75 MHz, CDCl3): δ = 45.35 (CHI), 35.12 (4-CH2), 37.90 (3-CH2), 56.48 (OCH3), 78.50 (2-CH), 126.05, 128.36, 142.06 (C arom.).


2-Iodo-1-methoxy-4-phenylbutane (10)

1H NMR (300 MHz, CDCl3): δ = 2.05 (m, 2 H, 3-CH2), 2.81 (m, 2 H, 4-CH2), 3.29 (s, 3 H, OCH3), 3.58 (m, 1 H, 2-CH), 4.05 (m, 2 H, 1-CH2), 7.12–7.25 (m, 5 H arom.).

13C NMR (75 MHz, CDCl3): δ = 33.05 (CHI), 35.12 (4-CH2), 37.90 (3-CH2), 58.48 (OCH3), 78.11 (C1H), 126.05, 128.36, 142.06 (C arom.).

Scheme 6
Iodomethylation of Alkenes with Reagent 4 and Iodine in MeOH: General Procedure

Iodine (0.27 g, 1.05 mmol) was added to the solution of reagent 4 (0.35 g, 1 mmol) in MeOH (4.0 mL) and the mixture was stirred for 5 min at r.t. The resulting mixture was added to a solution of alkene (2.0 mmol) in MeOH (2.0 mL) and stirred at r.t. for 10 min. The reaction mixture was washed with 5% NaHCO3 (30 mL), treated with Et3O (2 × 30 mL), and the Et3O extract was washed with water and sat. solution of NaCl and dried with Na2SO4. The aqueous solution that was left after extraction, was acidified with HNO3 and the white precipitate of sodium salt of 3-iodobenzoic acid was separated by filtration and used for regeneration of reagent 4. The Et3O solution was concentrated and the residue was dissolved in hexane (3.0 mL) and separated by column chromatography on silica gel using hexane as the eluent. The isolated compounds 7a,b,d were identified by comparison of their spectra with literature data.*

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