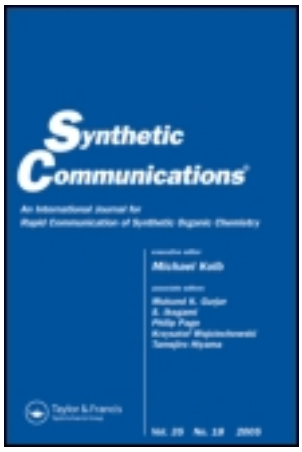

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(Dichloroiodo)benzene—An Easily Available Reagent for Chloro- and Iodoalkoxylation, Iodohydroxylation, and Iodochlorination of Alkenes

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(Dichloroiodo)benzene—An Easily Available Reagent for Chloro- and Iodoalkoxylation, Iodohydroxylation, and Iodochlorination of Alkenes

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ABSTRACT

A convenient synthesis of vicinal methoxychlorides, methoxyiodides, iodhydrines and iodocloride from alkenes using $PhICl_2/CH_3OH$, $I_2/PhICl_2/CH_3OH$, $I_2/PhICl_2/CH_3CN/H_2O$ and $I_2/PhICl_2/CH_2Cl_2$ is described.

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Key Words: (Dichloroiodo)benzene; Alkenes; Methoxychlorides; Methoxyiodides; Iohydrines.

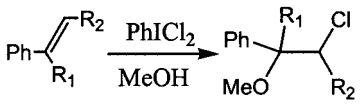
(Dichloroiodo)benzene is known as a good reagent for chlorination and oxidation of various organic compounds.[1–3] It is also an effective mediator of addition reactions to triple and double bonds. Recently the Moriarty group has found that the combination of $PhICl_2$ and lead(II) thiocyanate provides stereoselective 1,2-dithiocyanation of alkynes[4] and α-thiocyanation of silyl enol ethers, silyl ketene acetals and β-dicarbonyl compounds.[5]

We have found, that the $PhICl_2$ in reactions with alkenes in MeOH at room temperature easily forms products of electrophilic chloromethoxylation, but in presence of iodine processes of iodomethoxylation, iodohydroxylation, or iodochlorination take place. In general, synthesis of alkoxychlorides and alkoxybromides or corresponding halohydrins from alkenes is a well-established preparative procedure. However, direct synthesis of methoxychlorides, methoxyiodides and iodohydrins from olefins is often difficult to achieve.

$PhICl_2$ easily reacts with aromatic alkenes (**1**–**3**) in MeOH at room temperature,[6] giving the chloromethoxy derivative (**4**–**6**) with 68–90% preparative yields (Sch. 1, Table 1). This reaction is typical electrophilic anti-addition process, since the mixture of *erythro*-/*treo*-diastereoisomers **5** in a ratio 64 : 36% is formed from *E*-stilbene.

Side process is observed only in the case of α-methylstyrene (**7**), when besides a product of addition **8**, the product of chlorination of methyl groups (**9**) is formed (Sch. 2). Compounds **8** and **9** could not be separated by flash chromatography under a variety of conditions: these compounds were obtained in a yield of 70% and in a ratio of approximately 75 : 25% as judged from GC-MS and NMR spectra.

The product **9** is result of the minor contribution of the free-radical chlorination methyl group of compound **8** (or parent α-methylstyrene **7**) under action of $PhICl_2$ which is known as a reagent of chlorination alkane.[2,3]



1-3 **4-6**

R_1=R_2=H (**1**,**4**), Ph (**2**,**5**); R_1=Ph, R_2=H (**3**,**6**)

Scheme 1.

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Table 1. Synthesis of methoxychlorides, methoxyiodides, iodohydrines and iodochloride by reaction of alkenes with $PhICl_2$ or $I_2/PhICl_2$ in different medium.

Substrate	Product	Reaction conditions[a]	Yield,[b] %
1	**4**	$PhICl_2$/MeOH	68
2	**5**	$PhICl_2$/MeOH	90
3	**6**	$PhICl_2$/MeOH	72
1	**12**	$I_2/PhICl_2$/MeOH	80
3	**13**	$I_2/PhICl_2$/MeOH	94
7	**14**	$I_2/PhICl_2$/MeOH	91
10	**15**	$I_2/PhICl_2$/MeOH	78
11	**16**	$I_2/PhICl_2$/MeOH	78
1	**17**	$I_2/PhICl_2/CH_3CN/H_2O$[c]	88
3	**18**	$I_2/PhICl_2/CH_3CN/H_2O$	95
7	**19**	$I_2/PhICl_2/CH_3CN/H_2O$	93
1	**20**	$I_2/PhICl_2/CH_2Cl_2$	84

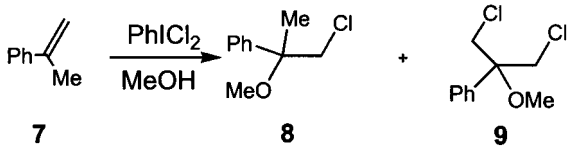
[a]Reaction at r.t. and in during 30 min.
[b]Yield of isolated pure product.
[c]CH_3CN (5 mL)/H_2O (1 mL) for 1.0 mmol of alkene.

At the same time, reaction of $PhICl_2$ with alkenes (**1**, **3**, **7**, **10**, **11**) in the presence of iodine in MeOH has another pathway, easily giving products of the iodomethoxylation of double bonds with 78–94% yield (Sch. 3).

When cyclohexene (**10**) in MeOH was reacted with $PhICl_2$ in the presence of iodine at room temperature, a major product of the reaction is *trans*-1-iodo-2-methoxycyclohexane (**15**) in 78% preparative yield. Therefore the reaction has a high *trans*-stereoselectivity and anti-addition character.

It is important to note, that at iodomethoxylation of the alkenes under action of $I_2/PhICl_2$ halogenation of methyl groups does not take place in difference from chloromethoxylation (see above).

Stilbene (**2**) was practically inert to action of $I_2/PhICl_2$ while it is shown above, the chloromethoxylation reaction proceeds with a high yield. Probably,



7 **8** **9**

Scheme 2.

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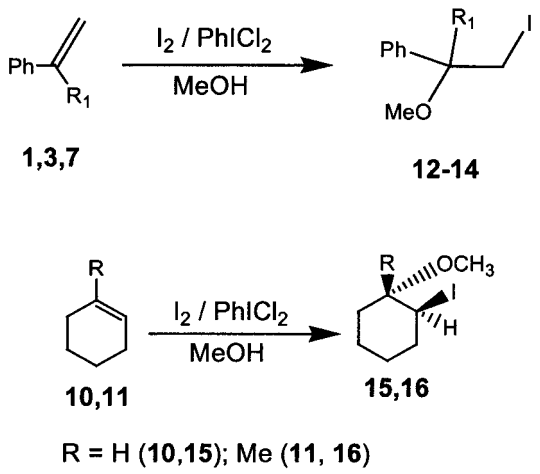
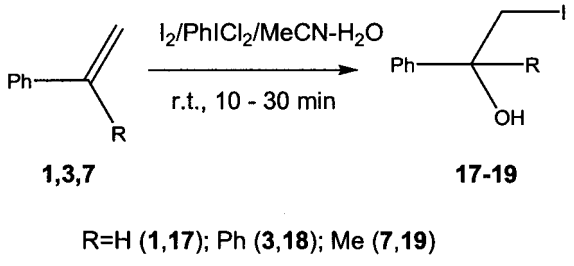


Scheme 3.

phenyliodosodichloride acts as an oxidizer of iodine up to electrophilic iodine intermediates—ICl or CH_3OI. These intermediates possess lower electrophilic activity, than intermediates, formed in the case of the chloromethoxylation (for example, Cl_2, or CH_3OCl). In this connection we can note, that stilbene (**2**) was inert also to action of *tert*-butylhypoiodide, formed from *tert*-BuOK and iodine monochloride.[7]

When reaction of $I_2/PhICl_2$ with alkenes **1**, **3**, and **7** was carried out in CH_3CN-H_2O mixture instead of methanol, corresponding iodohydrins **17–19** were obtained with 88–95% yields (Sch. 4).

Preparation of iodohydrins from alkenes and the organic derivative of polyvalent iodine-phenyliodine(III) bistrifluoroacetate is known.[8] But in this case is necessary to use 0.7–1.0 equivalents of expensive $PhI(OCOCF_3)_2$ on



Scheme 4.

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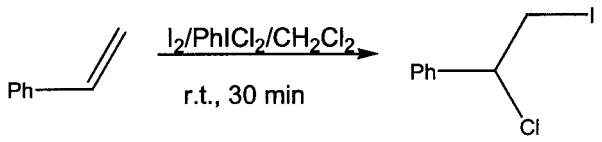

1 20

Scheme 5.

0.6 equivalent of the alkene (**8**). In our case it is required only 0.52 equivalents of the more accessible $PhICl_2$ on 1.0 equivalent of the alkene.

In the absence of oxygen-containing nucleophiles under action of I_2/$PhICl_2$ in CH_2Cl_2 on styrene (**1**) iodochlorination reaction takes place and 1-chloro-2-iodophenylethane (**20**) is formed in good yield (84%) (Sch. 5). Earlier similar iodochlorination was observed with use of $KICl_2$, but this reagent has shown lower regioselectivity and formed >15% of the regioisomer of compound (**20**).[9]

In the case of reaction of α-methylstyrene (**7**) with $I_2/PhICl_2$ in CH_2Cl_2 iodochlorination proceeds also easily, but prepared product was not isolated preparatively, since it decomposes at insignificant heating or action of a daylight, especially during attempts of separating by the flash chromatography.

Finally, our results demonstrate that (dichloroiodo)benzene is accessible, general, and effective reagent for chloro- and iodomethoxylation, iodohydroxylation or iodochlorination of alkenes. Especially it would be noteworthy that these processes does not require any special condition (inert atmosphere, anhydrous solvents and reagents), and proceeds at room temperature within 30 min in good yields.

EXPERIMENTAL

Elemental analysis was carried out on an E.A. 1106 Carlo Erba CHNS-O instrument. Mass spectra were recorded using a Finnigan MAT-8200 mass spectrometer. ^1H and ^{13}C NMR spectra recorded on a Bruker AC-200 (200.13 and 50.32 MHz), AM-300 (300.13 and 75.47 MHz), AM-400 (400.13 and 100.61 MHz), DRX-500 (500.13 and 125.76 MHz) spectrometer.

Typical procedure. 2-Iodo-1-methoxy-1-phenylethane (12). To a mixture of (dichloroiodo)benzene (289 mg, 1.05 mmol) and iodine (280 mg, 1.1 mmol) in MeOH (8.0 mL) was added at room temperature styrene (**1**) (208 mg, 2.0 mmol) in MeOH (2 mL). The resulting solution was stirred at

room temperature for 10 min. The reaction mixture was poured into 1% aq $Na_2S_2O_3$ (20 mL) and extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with water (50 mL) and brine (30 mL), and dried with Na_2SO_4. The organic solvents were evaporated in vacuo and the residual products were purified by flash chromatography (hexane, after hexane/benzene) with silica gel to give the product **12** (420 mg in 80% yield as an oil (lit. [10], oil). ^{1}H NMR (400 MHz, CCl_4-$(CD_3)_2CO$-3 : 1, TMS, δ, ppm, J, Hz): 3.21 (s, 3H, OCH_3), 3.23 (m, 2H, CH_2), 4.21 (dd, 1H, J = 5.0, 8.0), 7.26–7.34 (m, 5H$_{arom.}$). ^{13}C NMR (100 MHz, ppm, CCl_4-$(CD_3)_2CO$–3 : 1, δ, ppm): 10.10 (CH_2I), 56.94 (OCH_3), 83.55 (*C*H-OCH_3), 126.51, 128.23, 128.53, 139.98 (C_{arom}). HRMS (m/z): Calcd. for $C_9H_{11}IO$: 261.98564. Found: 261.98537. MS (EI, 70 eV): 262 (<1), 135 (14), 121 (100), 104 (10), 103 (9), 91 (10), 77 (13) amu.

1-Methoxy-1,1-diphenyl-2-iodoethane (13). m.p. 85–86°C. ^{1}H NMR (500 MHz, CCl_4-$CDCl_3$–3 : 1, CHS, δ, ppm): 3.12 (s, 3H, OCH_3), 4.08 (s, 2H, CH_2), 7.21 (t, 2H$_{arom}$) 7.27(t, 4H$_{arom.}$), 7.34 (d, 4H$_{arom}$). ^{13}C NMR (125 MHz, CCl_4-$CDCl_3$–3 : 1, δ): 15.34 (CH_2-I), 50.02 (OCH_3), 80.51 (*C*HOCH_3), 127.13, 127.26, 127.98, 142.92 (C_{arom}). Calcd. for $C_{15}H_{15}IO$: C 53.27%, H 4.47%, I 37.53%. Found: C 53.72%, H 4.34%, I 37.47%. HRMS (m/z): Calcd. for $C_{15}H_{15}IO$: 338.01694. Found: 338.01713.

1-Iodo-2-methoxy-2-phenylpropane (14). oil. ^{1}H NMR (500 MHz, CCl_4-$CDCl_3$–3 : 1, CHS, δ, ppm, J, Hz): 1.69 (s, 3H, CH_3), 3.11 (s, 3H, OCH_3), 3.37 (d, 1H$_a$, J = 10.0), 3.46 (d, 1H$_b$, J = 10.0), 7.25 (t, 1H$_{arom}$) 7.32(t, 2H$_{arom.}$), 7.37 (d, 2H$_{arom}$). ^{13}C NMR (125 MHz, CCl_4-$CDCl_3$–3 : 1, δ, ppm): 19.25 (*C*H_2-I), 23.85 (CH_3), 51.14 (O*C*H_3), 76.87 (*C*-OCH_3), 126.27, 127.69, 128.44, 141.50 (C_{arom}). Calcd. for $C_{10}H_{13}IO$: C 43.50%, H 4.75%, I 43.96%. Found: C 43.48%, H 4.67%, I 45.83%. HRMS (m/z): Calcd. for $C_{10}H_{13}IO$: 276.00129. Found: 276.00142. MS (EI, 70 eV): 276 (<1), 261 (<1), 149 (14), 148 (49), 135 (75), 118 (74), 105 (57), 91 (63), 77 (58).

***trans*-1-Iodo-2-methoxycyclohexane (15)**. oil. ^{1}H NMR (200 MHz, CCl_4-$CDCl_3$–3 : 1, TMS, δ, ppm, J, Hz): 3.16 (ddd, 1H, J = 8.2, 8.2, 4.0), 3.31 (s, OCH_3), 3.99 (ddd, 1H, J = 9.8, 8.1, 4.2). ^{13}C NMR (50 MHz, CCl_4-$CDCl_3$–3 : 1, TMS, δ, ppm): 23.10, 26.44, 29.58, 34.19 (*C*H-I), 36.81, 56.56 (OCH_3), 83.32 (*C*H-OCH_3). Calcd. for $C_7H_{13}IO$: C 35.02%; H 5.46%; I 52.86%. Found: C 35.24%; H 5.36%; I 52.46%.

***r*-2-iodo-t-1-methoxy-1-methylcyclohexane (16)**. oil. ^{1}H NMR (200 MHz, CCl_4-$CDCl_3$–3 : 1, TMS, δ, ppm, J, Hz): 1.27 (s, CH_3), 3.15 (s, OCH_3), 4.29 (dd, 1H, J = 8.2, 4.0). ^{13}C NMR (50 MHz, CCl_4-$CDCl_3$–3 : 1, TMS, δ, ppm): 22.10 (CH_3), 23.38, 25.56, 32.48, 35.29 (*C*H_2-I), 41.42, 48.60 (OCH_3), 75.30 (*C*H-OCH_3). HRMS (m/z): Calcd. for $C_8H_{15}IO$: 254.01694. Found: 254.01840. MS (EI, 70 eV, I(%)): 254 (<1), 127 (31), 97 (34), 95 (37), 85 (54), 71 (63), 57 (100), 43 (85).

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2-Iodo-1-phenylethanol (17). oil. ^{1}H NMR (200 MHz, CCl_4-$CDCl_3$–3 : 1, TMS, δ, ppm, J, Hz): 3.31 (s, 1H, OH), 3.37 (m, 2H, H-2), 4.73 (dd, 1H, $J = 4.1, 8.2$), 7.30 (s, $5H_{arom}$). ^{13}C NMR (50 MHz, CCl_4-$CDCl_3$–3 : 1, TMS, δ, ppm): 14.62 (CH_2-I), 73.73 (CH-OH), 125.63, 127.97, 128.33, 141.18 (C_{arom}).

2-Iodo-1,1-diphenylethanol (18). oil. ^{1}H NMR (300 MHz, (-$(CD_3)_2CO$, CHS, δ, ppm, J, Hz): 1.70 (s, 3H, CH_3), 2.96 (s, 1H, OH), 3.63 (d, $1H_a$, $J = 12.5$), 3.67 (d, $1H_b$, $J = 12.5$), 7.33 (m, $1H_{arom}$) 7.54 (m, $2H_{rom.}$), 7.56 (d, $2H_{arom}$). ^{13}C NMR (75 MHz, -$(CD_3)_2CO$, δ, ppm): 23.86 (CH_2-I), 29.40 (CH_3), 72.79 (C-OH), 126.00, 127.69, 128.79, 146.20 (C_{arom}). Calcd. for $C_9H_{11}IO$: C 41.24%, H 4.23%. Found: C 41.48%, H 4.16%.

1-Iodo-2-phenylpropan-2-ol (19). oil. ^{1}H NMR (300 MHz, (-$(CD_3)_2$-CO, CHS, δ, ppm): 4.18 (s, 2H, CH_2-OH), 5.47 (s, 1H, OH), 7.33 (m, $2H_{arom}$) 7.39 (m, $4H_{arom.}$), 7.54 (d, $4H_{arom}$). ^{13}C NMR (75 MHz, -$(CD_3)_2CO$, δ, ppm): 21.90 (CH_2-I), 114.67 (C-OH), 127.10, 127.86, 128.72, 128.87, 128.97, 129.18, 146.05 (C_{arom}). Calcd. for $C_{14}H_{13}IO$: C 51.87%, H 4.04%. Found: C 51.34%, H 4.26%.

1-Chloro-2-iodo-1-phenylethane (20). 44–45°C (lit.[11] 42–43°C). ^{1}H NMR (200 MHz, CCl_4-$CDCl_3$–3 : 1, TMS, δ, ppm, J, Hz): 3.80 (m 2H, H-2), 5.11 (dd, 1H, H-1, $J = 6.0, 9.2$), 7.42 (s, $5H_{arom}$). ^{13}C NMR (50 MHz, CCl_4-$CDCl_3$–3 : 1, TMS, δ, ppm): 9.80 (CH_2-I), 61.39 (CH-Cl), 127.05, 128.52, 128.85, 138.96 (C_{arom}).

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