Rhodium(II)-Catalyzed Reaction of Iodonium Ylides with Heterocyclic and Aromatic Compounds. Efficient Synthesis of Fused Acetals and C-H Insertion Products

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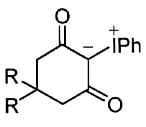
Introduction

Iodonium ylides are attractive and important reagents in organic synthesis.[1] Iodonium ylides are also used as synthetic equivalents of the corresponding diazo compounds. Photochemical and metal-mediated reactions of iodonium ylides with several substrates have been widely studied by several groups.[2] The reactions include C-H and N-H insertions,[3] Wolff-rearrangement,[4] cyclopropanation,[5] and cycloaddition.[6] We have interested in rhodium(II)-catalyzed reactions of iodonium ylides with heterocycles and aromatic compounds. We report here our results on rhodium(II)-catalyzed reactions of iodonium ylides with a variety of heterocycles and aromatic compounds.

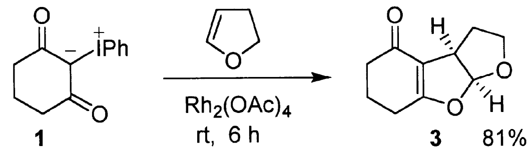
Results and Discussion

Iodonium ylides **1-2** were prepared by the reaction of the corresponding 1,3-dicarbonyl compounds with iodobenzene diacetate according to Koser's method in 81 and 80% yields, respectively.[7] Iodonium ylides **1-2** are fairly stable and can be stored in a refrigerator for a year.



1 R=H
2 R=CH_3

Reactions with dihydrofuran were first examined. When iodonium ylide **1** was treated with 2,3-dihydrofuran as a solvent and a reactant at room temperature for 6 h in the presence of 1 mol % of $Rh_2(OAc)_4$, cycloadduct **3** was obtained in an 81% yield (Scheme 1). Support for the structural assignment comes from spectroscopic analysis. The *cis*-stereochemistry of **3** is supported by the coupling constant (J = 5.9 Hz) at δ = 6.19 due to acetal methine proton. Similarly, reaction of **2** with dihydrofuran afforded the fused acetal **4** in 88% yield. The fused acetals are very important as a structural subunit of a variety of biologically active natural products such as aflatoxins,[8] dendrillolide,[9] clerodin,[10] asteltoxin,[11] rhyacophiline,[12] and paraherquonin.[13] The application of the fused acetals to natural aflatoxin B_2 and unnatural demethoxyaflatoxin B_2 has been reported.[14]



Scheme 1

With furan, cycloadducts **5-6** were also produced in 51 and 56% yields, respectively. The reaction with 2,5-dimethylfuran gives a higher yield. For example, treatment of **1** and **2** with 2,5-dimethylfuran afforded cycloadducts **7-8** in 83 and 95% yields, respectively. With neat dihydropyran, cycloaddition was also successful. Reactions with dihydropyran afforded cycloadducts **9-10** in 89 and 93% yields, respectively. The stereochemistry of **9** and **10** is also assigned as *cis* by spectral analysis and by the analogy with the earlier reported data.[15] The results are summarized in Figure 1. Although several syntheses of fused acetals mediated by manganese(II) acetate,[15] ceric ammonium nitrate,[16] and tetrabutylammonium peroxydisulfate[17] have been already reported, our technique has the advantage of mild and catalytic reaction conditions, no work-up, and high yield.

In order to compare with the corresponding furan, thiophenes were next examined. Treatment of **1** with thiophene at room temperature for 6 h in the presence of 1 mol % of $Rh_2(OAc)_4$ afforded the C-H insertion product **11**, without formation of the expected cycloadduct, in a 71% yield (Scheme 2). The assignment of **11** is clearly confirmed by ^{1}H NMR absorption peaks at δ = 7.44 (d, J = 5.2 Hz), 7.09 (dd, J = 5.2, 3.5 Hz), and 7.00 (d, J = 3.5 Hz). Similarly, reaction of **2** with thiophene gave the 2-substituted product **12** in a 75% yield (Figure 2). The formation of the 2-substituted

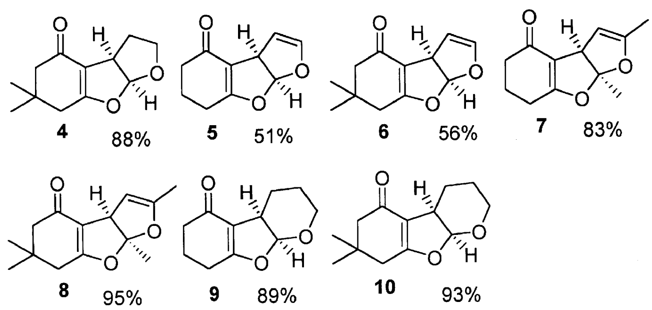
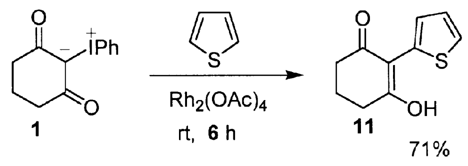


Figure 1



Scheme 2

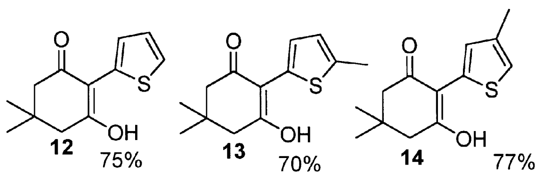
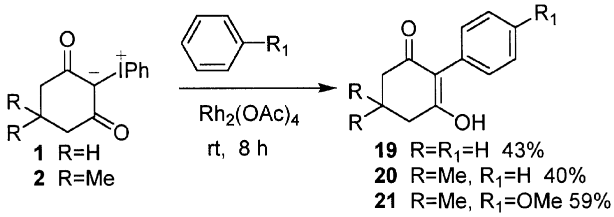


Figure 2

products is very surprising in comparision to the reported results that the rhodium(II)-catalyzed reaction of diazodicarbonyl compounds with thiophene gave exclusively the 3-substituted product.[18] Unsymmetrical thiophene was also investigated. Reaction of **2** with 2-methylthiophene afforded 2-substituted product **13** in 70% yield. Similarly, reaction of **2** with 3-methylthiophene gave the 2-substituted product **14** in a 77% yield. These results show that the reaction with unsymmetrical thiophenes occurs exclusively at the unsubstituted double bond.

Although the exact mechanism of the reaction is still not clear, it is best described as shown in Scheme 3. The iodonim ylide **1** first gives a carbene **15** by expulsion of iodobenzene by $Rh_2(OAc)_4$. Intermediate **15** is trapped by the double bond of heterocyles to give cyclopropane 1**6**, which undergoes bond cleavage at the 2- or 3-position to give ziwitterions **17** and **18**. Ring closure of **17** gives the cycloadduct **3** and proton transfer of **18** gives C-H insertion product **11**.

Finally, the rhodium-catalyzed reactions with aromatic compounds such as benzene and anisole were examined using 1 mol % of $Rh_2(OAc)_4$. Treatment of **1** and **2** with benzene at room temperature for 8 h gave the C-H insertion products **19** and **20** in 43 and 40% yields, respectively (Scheme 4). With more electron-rich anisole, C-H insertion product **20** were produced in increased yield (59%). In this case, no cycloaddition and *ortho*-substituted product were found. This reaction also provides a rapid synthetic route toward 3-hydroxy-2-phenyl-cyclohex-2-enone derivatives.



Scheme 4

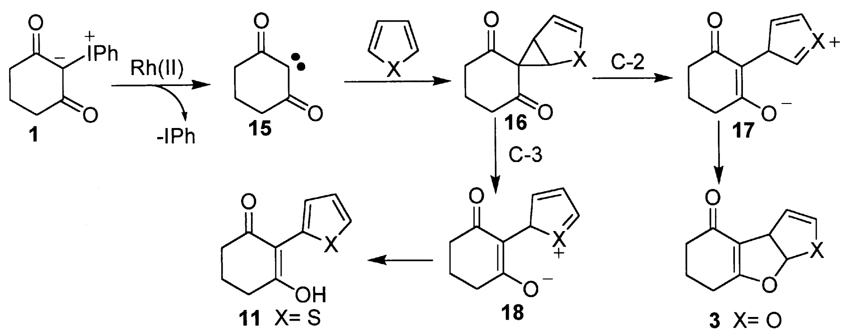
In conclusion, the reactions of iodonium ylides with heterocycles and aromatic compounds have been carried out in the presence of 1 mol % of rhodium(II) acetate. These reactions provide a rapid synthetic entry into polyheterocycles such as fused acetals and C-H insertion products.

Experimental Section

All experiments were carried out under nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). Melting points were determined with microcover glasses on a Fisher-Johns apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Model ARX (300 MHz) spectrometer. IR spectra were recorded on a JASCO FTIR 5300 spectrophotometer. High resolution mass (HRMS) spectra were obtained on JEOL JMS-700 spectrometer at Korea Basic Science Institute.

2,3,3a,6,7,8a-Hexahydro-5*H*-1,8-dioxa-cyclopenta[*a*]inden-4-one (3). To a solution of iodonium ylide **1** (314 mg, 1.0 mmol) and 2,3-dihydrofuran (3 mL) was added rhodium acetate (5 mg, 0.01 mmol) at room temperature under N_2. The reaction was allowed to continue stirring for 6 h. Evaporation and purification by silica gel chromatography with 2 : 1 hexane:ethyl acetate as eluent afforded **3** (146 mg, 81%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (1H, d, J = 5.9 Hz), 4.07 (1H, m), 3.67 (1H, m), 3.60 (1H, m), 2.43 (2H, m), 2.31 (2H, m), 2.02 (2H, m); IR (neat) 2951, 1634, 1454, 1406, 1368, 1244, 1181, 1086, 951, 900 cm^{-1}; HRMS m/z (M$^+$) calcd for $C_{10}H_{12}O_3$: 180.0783. Found: 180.0786.

6,6-Dimethyl-2,3,3a,6,7,8a-hexahydro-5*H*-1,8-dioxa-cyclo-



Scheme 3

penta[*a*]inden-4-one (4). Reaction of iodonium ylide **2** (342 mg, 1.0 mmol) and 2,3-dihydrofuran (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **4** (183 mg, 88%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (1H, d, *J* = 5.8 Hz), 4.08 (1H, m), 3.70 (1H, m), 3.61 (1H, m), 2.32 (2H, s), 2.20 (2H, s), 2.06 (2H, m), 1.08 (3H, s), 1.06 (3H, s); IR (neat) 2959, 2876, 1634, 1406, 1364, 1248, 1227, 1148, 1082, 1035, 949, 923, 883 cm^{-1}.

3a,6,7,8a-Tetrahydro-5*H*-1,8-dioxa-cyclopenta[*a*]inden-4-one (5). Reaction of iodonium ylide **1** (314 mg, 1.0 mmol) and furan (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **5** (91 mg, 51%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (1H, d, *J* = 7.5 Hz), 6.35 (1H, dd, *J* = 2.6, 2.1 Hz), 5.35 (1H, dd, *J* = 2.6, 2.5 Hz), 4.26 (1H, m), 2.47 (2H, m), 2.31 (2H, m), 2.01 (2H, m); IR (neat) 3109, 2994, 2942, 1636, 1400, 1287, 1238, 1225, 1182, 1136, 1121, 1046, 1017, 980, 909 cm^{-1}.

6,6-Dimethyl-3a,6,7,8a-tetrahydro-5*H*-1,8-dioxa-cyclopenta[*a*]inden-4-one (6). Reaction of iodonium ylide **2** (342 mg, 1.0 mmol) and furan (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **6** (115 mg, 56%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (1H, d, *J* = 7.4 Hz), 6.35 (1H, dd, *J* = 2.6, 2.2 Hz), 5.34 (1H, dd, *J* = 2.6, 2.4 Hz), 4.27 (1H, m), 2.32 (2H, s), 2.23 (1H, d, *J* = 16.2 Hz), 2.14 (1H, d, *J* = 16.2 Hz), 1.07 (3H, s), 1.03 (3H, s); IR (neat) 3108, 2932, 1645, 1400, 1360, 1284, 1214, 1040, 977, 927 cm^{-1}.

2,8a-Dimethyl-3a,6,7,8a-tetrahydro-5*H*-1,8-dioxa-cyclopenta[*a*]inden-4-one (7). Reaction of iodonium ylide **1** (314 mg, 1.0 mmol) and 2,5-dimethylfuran (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **7** (171 mg, 83%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (1H, s), 3.88 (1H, s), 2.43 (2H, m), 2.30 (2H, m), 2.00 (2H, m), 1.78 (3H, s), 1.63 (3H, s); IR (neat) 2946, 1678, 1640, 1390, 1292, 1116, 997 cm^{-1}; HRMS m/z (M^+) calcd for $C_{12}H_{14}O_3$: 206.0939. Found: 206.0943.

2,6,6,8a-Tetramethyl-3a,6,7,8a-tetrahydro-5*H*-1,8-dioxa-cyclopenta[*a*]inden-4-one (8). Reaction of iodonium ylide **2** (342 mg, 1.0 mmol) and 2,5-dimethylfuran (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **8** (223 mg, 95%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (1H, s), 3.89 (1H, s), 2.30 (2H, s), 2.18 (2H, s), 1.79 (3H, s), 1.07 (3H, s), 1.04 (3H, s); IR (neat) 2959, 1680, 1634, 1402, 1294, 1240, 1177, 1117, 1074, 1028, 941, 912 cm^{-1}.

3,4,4a,7,8,9a-Hexahydro-2*H*,6*H*-1,9-dioxa-fluoren-5-one (9). Reaction of iodonium ylide **1** (314 mg, 1.0 mmol) and 3,4-dihydro-2*H*-pyran (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **9** (173 mg, 89%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (1H, d, *J* = 7.7 Hz), 3.67 (2H, m), 3.03 (1H, m), 2.41 (2H, m), 2.28 (2H, m), 1.96 (2H, m), 1.82 (2H, m), 1.71 (2H, m); IR (neat) 2948, 1633, 1454, 1404, 1232, 1184, 1115, 1061, 1042, 1001, 920 cm^{-1}.

7,7-Dimethyl-3,4,4a,7,8,9a-hexahydro-2*H*,6*H*-1,9-dioxa-fluoren-5-one (10). Reaction of iodonium ylide **2** (342 mg, 1.0 mmol) and 3,4-dihydro-2*H*-pyran (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **10** (207 mg, 93%) as a solid: 94-95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (1H, d, *J* = 7.7 Hz), 3.79 (1H, m), 3.10 (1H, m), 2.32 (2H, m), 2.22 (2H, m), 1.87 (2H, m), 1.65 (2H, m), 1.09 (3H, s), 1.07 (3H, s); IR (KBr) 2957, 1634, 1404, 1225, 1115, 1047, 918 cm^{-1}.

3-Hydroxy-2-thiophen-2-yl-cyclohex-2-enone (11). Reaction of iodonium ylide **1** (314 mg, 1.0 mmol) and thiophene (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **11** (138 mg, 71%) as a solid: m.p 178-180 °C; ^{1}H NMR (300 MHz) δ 7.44 (1H, d, *J* = 5.2 Hz), 7.09 (1H, dd, *J* = 5.2, 3.5 Hz), 7.00 (1H, d, *J* = 3.5 Hz), 6.69 (1H, s), 2.63 (2H, m), 2.50 (2H, m), 2.05 (2H, m); IR (KBr) 2928, 1572, 1313, 1198, 1080, 988 cm^{-1}; HRMS m/z (M^+) calcd for $C_{10}H_{10}O_2S$: 194.0398. Found: 194.0402.

3-Hydroxy-5,5-dimethyl-2-thiophen-2-yl-cyclohex-2-enone (12). Reaction of iodonim ylide **2** (342 mg, 1.0 mmol) and thiophene (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **12** (167 mg, 75%) as a solid: 204-205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, d, *J* = 5.2 Hz), 7.09 (1H, dd, *J* = 5.2, 3.4 Hz), 7.01 (1H, d, *J* = 3.4 Hz), 6.66 (1H, s), 2.49 (2H, s), 2.38 (2H, s), 1.13 (6H, s); IR (KBr) 2962, 1582, 1520, 1470, 1433, 1373, 1256, 1225, 1157, 1123, 1022, 885 cm^{-1}.

3-Hydroxy-5,5-dimethyl-2-(5-methyl-thiophen-2-yl)-cyclohex-2-enone (13). Reaction of iodonium ylide **2** (342 mg, 1.0 mmol) and 2-methylthiophene (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **13** (165 mg, 70%) as a solid: 168-172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (1H, d, *J* = 3.4 Hz), 6.72 (1H, d, *J* = 3.4 Hz), 6.67 (1H, s), 2.47 (5H, s), 2.36 (2H, s), 1.12 (6H, s); IR (KBr) 2957, 1562, 1464, 1366,1308, 1262, 1225, 1155, 1024, 1010, 876 cm^{-1}; HRMS m/z (M^+) calcd for $C_{13}H_{16}O_2S$: 236.0866. Found: 236.0871.

3-Hydroxy-5,5-dimethyl-2-(4-methyl-thiophen-2-yl)-cyclohex-2-enone (14). Reaction of iodonium ylide **2** (342 mg, 1.0 mmol) and 3-methylthiophene (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **14** (182 mg, 77%) as a solid: 160-162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (1H, s), 6.79 (1H, s), 6.59 (1H, s), 2. 48 (2H, s), 2.36 (2H, s), 2.25 (3H, s), 1.12 (6H, s); IR (KBr) 2957, 1572, 1329, 1260, 1204, 1146, 1028, 887, 862, 841 cm^{-1}; HRMS m/z (M^+) calcd for $C_{13}H_{16}O_2S$: 236.0866. Found: 236.0871.

3-Hydroxy-2-phenyl-cyclohex-2-enone (19). Reaction of iodonium ylide **1** (314 mg, 1.0 mmol) and benzene (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **19** (81 mg, 43%) as a solid: mp 139-141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (2H, dd, *J* = 7.7, 7.5 Hz), 7.36 (1H, t, *J* = 7.7 Hz), 7.18 (2H, d, *J* = 7.5 Hz); IR (KBr) 2953, 1568, 1302, 1192, 1145, 1078, 984, 909 cm^{-1}.

3-Hydroxy-5,5-dimethyl-2-phenyl-cyclohex-2-enone (20). Reaction of iodonium ylide **2** (342 mg, 1.0 mmol) and benzene (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **20** (87 mg, 40%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (2H, d, *J* = 7.8 Hz), 7.60 (1H, t, *J* = 7.5 Hz), 7.46 (2H, dd, *J* = 7.8, 7.5 Hz), 3.02 (2H, s), 2.57 (2H, s), 1.12 (6H, s); IR (neat) 2963, 1713, 1597, 1451, 1372, 1271, 1119, 1094, 934, 874 cm^{-1}; HRMS m/z (M^+) calcd for $C_{14}H_{16}O_2$: 216.1146. Found: 216.1150.

3-Hydroxy-2-(4-methoxy-phenyl)-5,5-dimethyl-cyclohex-2-enone (21). Reaction of iodonium ylide **2** (342 mg, 1.0 mmol) and anisole (3 mL) using rhodium acetate (5 mg, 0.01 mmol) as a catalyst afforded **21** (145 mg, 59%) as a solid: m.p 110-112 °C; ^{1}H NMR (300 MHz) δ 7.11 (2H, d, J = 8.8 Hz), 6.96 (2H, d, J = 8.8 Hz), 5.90 (1H, s), 3.80 (3H, s), 2.46 (2H, s), 2.35 (2H, s), 1.14 (6H, s); IR (KBr) 2961, 1712, 1599, 1512, 1372, 1246, 1177, 1032, 831 cm^{-1}; HRMS m/z (M^+) calcd for $C_{15}H_{18}O_3$: 246.1251. Found: 246.1256.

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