ORGANIC
LETTERS

2012
Vol. 14, No. 19
5078–5081

Oxidative Cleavage of α-Aryl Aldehydes Using Iodosylbenzene

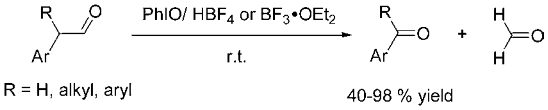
Nizam Havare and Dietmar A. Plattner*

Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg,
Albertstraße 21, D-79104, Freiburg im Breisgau, Germany

dietmar.plattner@chemie.uni-freiburg.de

Received August 21, 2012

ABSTRACT



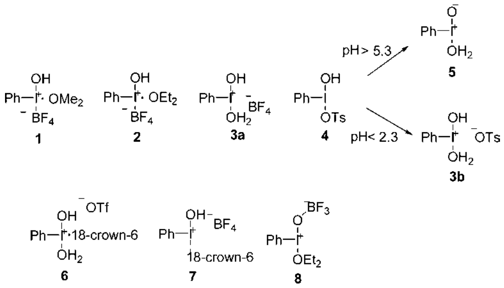
We found that α-aryl aldehydes can be cleaved to chain-shortened carbonyl compounds and formaldehyde by various iodosylbenzene complexes. A mechanistic scheme is presented that accounts for the loss of one carbon atom. Formaldehyde is further oxidized to CO and CO_2 under the reaction conditions.

Since the first synthesis of (dichloroiodo)benzene by Willgerodt et al. in 1886,[1] several new iodine(III) and iodine(V) reagents have been developed and are now used widely in organic synthesis, mainly because of their mild reaction conditions and their safe, simple, and low-cost preparation.[2] Reductive elimination from hypervalent λ^3- or λ^5-iodane intermediates results in oxidation, dehydrogenation, rearrangements, fragmentation reactions, etc.[2]

It is well-known that hypervalent λ^3-iodane reagents such as (diacetoxyiodo)benzene or protonated iodosylbenzene lead to oxidative C–C cleavage of glycols, epoxides, and unfunctionalized olefins, yielding the corresponding carbonyl compounds.[3–5] Koser et al. showed in 2004 that unfunctionalized olefins react with PhI(OH)(OTs) under oxidative rearrangement to the corresponding α-aryl ketones in excellent yields.[6]

Iodosylbenzene[7] is normally prepared from (diacetoxyiodo)-benzene and sodium hydroxide in aqueous media and reacted with HBF_4 (50–55% in diethyl ether or 48–50% in water) or with $BF_3 \cdot OEt_2$ to yield different labile complexes **1**, **2**, **3a**, and **8**[8–10] in different solvents. These and other iodosylbenzene-derivatized reagents **1**–**8** decompose at room temperature with different half-lives to give black tar and/or iodobenzene (Scheme 1).[8–10]

Scheme 1[a]



[a] Complexes **1** and **2** are stable for a few hours between −50 and −20 °C,[10a,b] while **3a**, **6**, and **7** are stable for a few days.[8a,b,10d] Complex **5** is formed as a neutral species through mildly alkaline conditions.[9a] Complexes **4**, **6**, and **7** are characterized by crystal structure analysis,[8b,9b,10d] and complex **8** is the proposed structure of reagent PhIO/$BF_3 \cdot OEt_2$.[10c]

---

(1) Willgerodt, C. *J. Prakt. Chem.* **1886**, *33*, 154.

(2) (a) Wirth, T., Ed. *Hypervalent Iodine Chemistry*; Topics in Current Chemistry 224; Springer: Berlin, 2003. (b) Varvoglis, A. *The Organic Chemisty of Polycoordinated Iodine*, 1st ed.; VCH: New York, 1992. (c) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*, 1st ed.; Academic Press: London, 1997. (d) Koser, G. F. Hypervalent halogen compounds. In: *The Chemistry of Functional Groups Supplement D*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1983; Chapter 18.

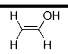
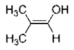
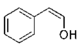
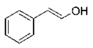
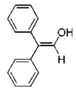
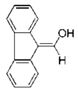
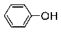
(3) For C–C oxidative cleavage of glycols, see: (a) Criegee, R.; Beuker, H. *Justus Liebigs Ann. Chem.* **1939**, *541*, 218. (b) Angyal, S. J.; Young, R. J. *J. Am. Chem. Soc.* **1959**, *81*, 5467. (c) Pausacker, K. H. *J. Chem. Soc.* **1953**, 107.

(4) Spyroudis, S.; Varvoglis, A. *J. Org. Chem.* **1981**, *46*, 5231.

(5) (a) Miyamoto, K.; Tada, N.; Ochiai, M. *J. Am. Chem. Soc.* **2007**, *129*, 2772. (b) Ochiai, M.; Miyamoto, K.; Yokota, Y.; Suefuji, T.; Shiro, M. *Angew. Chem.* **2005**, *117*, 77. *Angew. Chem., Int. Ed.* **2005**, *44*, 75. (c) Ochiai, M.; Miyamoto, K.; Shiro, M.; Tomoyuki, O.; Yamaguchi, K. *J. Am. Chem. Soc.* **2003**, *125*, 13006. (d) Koser, G. F.; Wettach, R. H.; Troup, J. M.; Frenz, B. A. *J. Org. Chem.* **1976**, *41*, 3609.

10.1021/ol301675v

Table 1. pK_E Values of Different Aromatic and Aliphatic Compounds Compared to Phenol

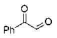
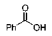
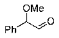
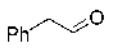
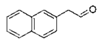
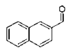
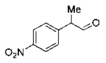
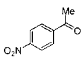
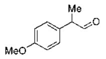
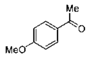
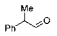
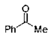
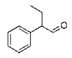
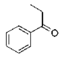
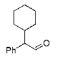
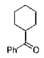
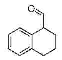
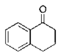
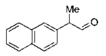
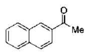
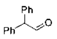
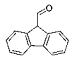
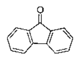
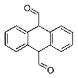
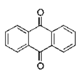
Entry	Enol	pK_E
1[13c]		6.23
2[13d]		3.86
3[13c]		3.35
4[13c]		3.07
5[13e]		0.98
6[13a,b]		-1.22
7[13f]		-13

We found that reagents **2**, **3a**, or **8** can be used for the transformation of α-aryl aldehydes to the corresponding C_1-shortened aldehydes or ketones, whereby the carbon atom is oxidized to CO and CO_2, respectively, in the process.

The enol content of simple aliphatic aldehydes is rather small.[11] In contrast, aromatic aldehydes display much lower pK_E values as compared to aliphatic aldehydes (see Table 1). The enol content can be determined by addition of halogen, and with that it is possible to calculate the equilibrium constant of the keto–enol tautomerism (K_E, pK_E).[12,13]

In the mechanistic scheme we derive from our experiment we assume that the oxidative cleavage proceeds most likely via the enol form. The studies show that α-trialkyl acetaldehydes such as pivalaldehyde (entry 1, Table 2) do not react with $PhIO/HBF_4$ (50–55% in diethyl ether, in absence of water) in accordance with the fact that they are lacking α-hydrogens.

Table 2[*,a,b]

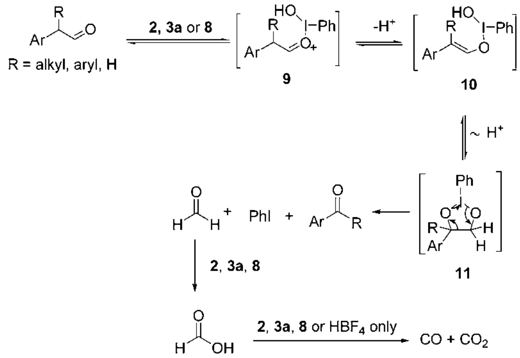
Entry	Substrate	Reagent	Method	Time	Product	Conver. (%)	Yield (%)
1		**2**	A1	5 days		no reaction	
2		**3a**	B1	24 h		100	72
3		**2**	A2	15 h		100	65[a]
4		**3a**	B2	6 days		100	98[b]
5		**3a**	B2	6 days		100	51
6		**8**	C2	26 h		88	63[a]
7		**2**	A2	10 days		47	42[a]
8		**8**	C1	44 h		82	40
9		**2**	B3	4.5 days		74	59
10		**8**	C1	2 h		100	57
11		**3a**	B2	3 days		100	39
12		**3a**	B2	5 days		100	42
13		**2**	A1	2.5 h		100	85
14		**2**	A1	2 h		100	70
15		**3a**	B1	24		100	87
16		**3a**	B1	1 day		100	91
17		**2**	A1	2 h		100	93

[*] Explanation of the reaction conditions: Method A1: The reaction was carried out with $PhIO/HBF_4 \cdot OEt_2$ (50–55% in diethyl ether) in abs CH_2Cl_2. Method A2: The reaction was carried out with $PhIO/HBF_4 \cdot OEt_2$ (50–55% in diethyl ether) in abs. 1,4-dioxane. Method B1: The reaction was carried out with $PhIO/HBF_4$ (48% in water) in CH_2Cl_2. Method B2: The reaction was carried out with $PhIO/HBF_4$ (48% in water) in 1,4-dioxane/water mixture (1:1). Method B3: The reaction was carried out with $PhIO/HBF_4$ (48% in water) in 1,4-dioxane. Method C1: The reaction was carried out with $PhIO/BF_3 \cdot OEt_2$ (48% in diethyl ether) in abs. CH_2Cl_2. Method C2: The reaction was carried out with $PhIO/BF_3 \cdot OEt_2$ (48% in diethyl ether) in abs 1,4-dioxane. [a] The yields were determined by GC analysis using internal standards (1,4-dichlorobenzene and *n*-heptane). [b] Isolated as 1-benzylidene-2-(2,4-dinitrophenyl)hydrazine.

The nonenolizable phenylglyoxal reacts with PhIO/HBF_4 (48% in water) to benzoic acid under C−C cleavage (entry 2, Table 2). Aryl aldehydes with a small enol content such as 2-methoxy-2-phenylethanol (entry 3, Table 2) do not give rise to the expected cleavage products: methyl benzoate is found as a side product in only 3% yield, but the main product is benzaldehyde in 65% yield. Unbranched α-aryl acetaldehydes react to the corresponding contracted aldehydes in good to excellent yield (entries 4 and 5, Table 2). α-Aryl alkyl aldehydes react to the corresponding ketones in good yields (entries 6−12, Table 2). The best yields are obtained with α,α-diaryl acetaldehydes as substrates (entries 13−17, Table 2), probably due to their low pK_E values. According to entries 6 and 7, Table 2, there is only a mild influence of donor and acceptor substituents on the reaction rates, the latter slowing down the reaction. In view of the fact that some of the iodane reagents are quite labile, some of the reaction times listed in Table 2 may seem surprisingly long. Experimental evidence leads us to assume that the lifetimes of the in situ prepared complexes depend strongly on the reaction conditions, especially if 1,4-dioxane is used as a solvent. We believe that 1,4-dioxane coordinates to the hypervalent iodane complex yielding longer lived species more akin in stability to **3a**, **6**, or **7**.

The reaction mechanism we thus propose is outlined in Scheme 2. We assume that intermediate **9** is first formed in equilibrium with the corresponding intermediate **10**. Under nucleophilic attack, a five-membered cyclic intermediate is formed. Precedence for the formation of the five-membered cyclic intermediate **11** is found in the literature for the decarboxylation of α-keto carboxylic acids[14a,b] and for the oxidative cleavage of acetophenone.[14c] Seemingly, the anion BF_4^- does not play a role in the outlined mechanism. We believe, however, that BF_4^- is of critical importance for the stability of the in situ formed reagents and thus for their overall reactivity toward the substrate aldehydes.

Scheme 2. Proposed Mechanism of the Oxidative Cleavage of α-Aryl Aldehydes with Iodosylbenzene Reagents



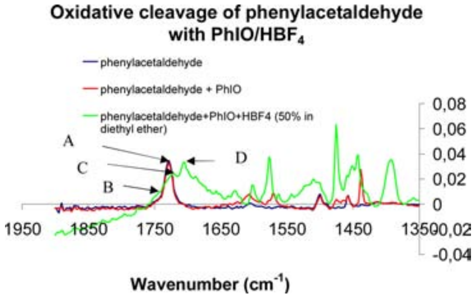


Figure 1. React-IR analysis of the reaction of phenylacetaldehyde with PhIO/HBF_4 (50−55% in diethyl ether) in dichloromethane. Carbonyl vibration of phenylacetaldehyde (A) (blue spectrum): 1728 cm^{-1}, formaldehyde (B), formic acid (C) and benzaldehyde (D) (green spectrum): 1743 cm^{-1}, 1720 cm^{-1} and 1705 cm^{-1}.

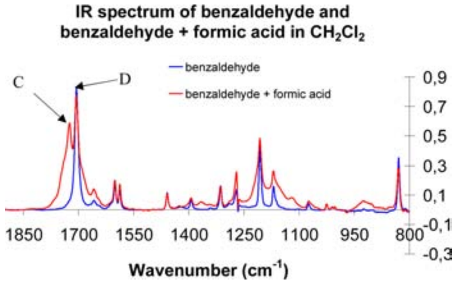


Figure 2. Reference spectrum of benzaldehyde and the mixture of benzaldehyde and formic acid in dichloromethane. Carbonyl vibration of benzaldehyde (D) (blue spectrum) and formic acid (C) (red spectrum): 1705 and 1724 cm^{-1} (the measuring accuracy of the react-IR^{TM} spectroscopy device is ±4 wave numbers). Carbonyl vibration of formaldehyde in the gas phase: 1743 cm^{-1}.[16]

---

(6) Justik, M. W.; Koser, G. F. *Tetrahedron Lett.* **2004**, *45*, 6159.

(7) Saltzman, H.; Sharefkin, J. G. *Org. Synth.* **1963**, *43*, 60.

(8) (a) Miyamoto, K.; Tada, N.; Ochiai, M. *J. Am. Chem. Soc.* **2007**, *129*, 2772. (b) Ochiai, M.; Miyamoto, K.; Yokota, Y.; Suefuji, T.; Shiro, M. *Angew. Chem.* **2005**, *117*, 77. *Angew. Chem., Int. Ed.* **2005**, *44*, 75. (c) Merritt, E. A.; Carneiro, V. M. T.; Silva, L. F.; Olofsson, B. *J. Org. Chem.* **2010**, *75*, 7416.

(9) (a) Richter, H. W.; Cherry, B. R.; Zook, T. D.; Koser, G. F. *J. Am. Chem. Soc.* **1997**, *119*, 9614. (b) Koser, G. F.; Wettach, R. H.; Troup, J. M.; Frenz, B. A *J. Org. Chem.* **1976**, *41*, 3609.

(10) (a) Zhdankin, V. V.; Tykwinski, R.; Caple, R.; Berglund, B.; Koz'min, A. S.; Zefirov, N. S. *Tetrahedron Lett.* **1988**, *29*, 3703. (b) Zhdankin, V. V.; Mullikin, M.; Tykwinski, R.; Berglund, B.; Koz'min, A. S. *J. Org. Chem.* **1989**, *54*, 2605. (c) Ochiai, M.; Varvoglis, A.; Zhdankin, V. V.; Koser, G. F.; Wirth, T.; Tohma, H.; Kita, Y. *Top. Curr. Chem.* **2003**, *224*, 60. (d) Ochiai, M.; Miyamoto, K.; Shiro, M.; Ozawa, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **2003**, *125*, 13006.

(11) (a) Toullec, J. *Adv. Phys. Org. Chem.* **1982**, *18*, 1. (b) Kresge, A. J. *Chem. Tech* **1986**, 250.

(12) Fritz, J. S.; Hammond, G. S. *Quantitative Organic Analysis*; Wiley: New York, 1957.

(13) (a) Harcourt, M. P.; More O'Ferrall, R. A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1415. (b) Harcourt, M. P.; More O'Ferrall, R. A. *J. Chem. Soc., Chem. Commun.* **1987**, 822. (c) Toullec, J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, 1990. (d) Chiang, Y.; Kresge, A. J.; Walsh, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 6314. (e) Chiang, Y.; Kresge, A. J.; Krogh, E. T. *J. Am. Chem. Soc.* **1988**, *110*, 2600. (f) Capponi, N.; Gut, I.; Wirz, J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 344.

(14) (a) Moriarty, R. M.; Gupta, S. C.; Hu, H.; Berenschot, D. R.; White, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 686. (b) Moriarty, R. M.; Vaid, R. K.; Duncan, M. P.; Ochiai, M.; Inenaga, M.; Nagao, Y. *Tetrahedron Lett.* **1988**, *29*, 6913. (c) Moriarty, R. M.; Prakash, I.; Penmasta, R. *J. Chem. Soc., Chem. Commun.* **1987**, 202.

According to our mechanistic scheme, intermediate **11** fragments to the product, formaldehyde, and iodobenzene. Formaldehyde is oxidized to formic acid under these reaction conditions, which is then further oxidized to carbon monoxide and carbon dioxide (Scheme 2). In an independent study, we confirmed that formaldehyde and formic acid are oxidized to carbon monoxide and carbon dioxide under these conditions.

Carbon monoxide and carbon dioxide have been detected with $PdCl_2/HCl$[15a] and aqueous barium hydroxide solution,[15b] respectively. Formaldehyde and formic acid are too short-lived under these conditions to be detected by ^1H NMR spectroscopy of the authentic reaction mixtures. Formaldehyde and formic acid have been characterized in the reaction mixture by react-IR. The react-IR analysis with phenyl acetaldehyde as a substrate confirmed our suspicion that formaldehyde is first formed in the reaction and is then further oxidized to formic acid. The latter is then cleaved into carbon monoxide and carbon dioxide (Figures 1 and 2).

In summary, an efficient method for the oxidative cleavage of α-aryl aldehydes to the corresponding C_1-shortened aldehydes or ketones by using a combination of iodosylbenzene and HBF_4 was developed.

Acknowledgment. We thank Prof. Breit (University of Freiburg) for the kind permission to use his GC and react-IR equipment.

Supporting Information Available. Preparation of substrates, experimental details of the oxidative cleavage reactions, and ^1H NMR and GC/MS-EI data. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(15) (a) Allen, T. H.; Root, W. S. *J. Biol. Chem.* **1955**, *216*, 309. (b) *Brockhaus ABC Chemie*; Brockhaus: Leipzig, 1965; p 156.

(16) Vaccani, S.; Kühne, H.; Bauder, A. *Chem. Phys. Lett.* **1977**, *50*, 187.

The authors declare no competing financial interest.