Highly Chemoselective Hydrogenolysis of Iodoarenes

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The catalytic hydrodehalogenation reaction using molecular hydrogen and Pd/C has been revisited. It is shown that the speed of removal of halogen increases with increasing electronegativity I < Br < Cl. Nevertheless, selective dehydrohalogenation in compounds containing other reducible functions can be achieved only with iodine and not with bromine or chlorine. Selective deiodination of iodobenzophenone could be accomplished without reducing the carbonyl group. Hydrogenolysis of azidoiodoaromatic compounds to the corresponding azido compounds is high yielding. This selectivity was exploited for the labeling of benzophenone- and azido-containing compounds by deuterium and tritium.

Introduction

Selectivity in organic chemistry is a major asset during the synthesis of complex molecules, and the development of chemoselective reactions provides a powerful tool for organic chemists.[1] We have recently revisited the catalytic hydrogenolysis of iodoarenes using hydrogen and Pd/C.[2] We have shown that when an iodoaryl compound and an olefin were separately subjected to reducing conditions, the double bond was transformed faster. But, when these two groups were reacted together (whether borne by the same molecule or not), the selectivity obtained was unexpected. The less reactive iodoarene was selectively reduced while the more reactive double bond was unaffected. We have shown, for the first time, that the chemoselectivity of this reaction is controlled by the high affinity of the iodinated compound for the catalyst.

Herein we describe further results in the study of the hydrodehalogenation reaction, in particular concerning the effect on the chemoselectivity of varying the halogen (I, Br, Cl). We show that the chemoselectivity of this reaction versus double-bond hydrogenation strongly depends on the halogen. In addition, we demonstrate that the catalytic hydrogenolysis of iodoarenes is compatible with easily reducible functional groups such as benzophenone and aryl azide. We took advantage of this chemoselectivity to develop a general method to label benzophenone- and aryl azide-containing compounds with deuterium and tritium.

Results and Discussion

Hydrodehalogenation of chloro-, bromo-, and iodobenzene was carried out individually as well as in competitive reactions with *trans*-1-phenyl-1-propene, under the following conditions: methanol, 10% Pd/C, triethylamine (10 equiv), H_2 (1 atm). We first verified that the stirring speed was sufficiently high (1400 rpm) to ensure that the reduction occurred under kinetic conditions. When the reactions were carried out separately, the reduction of *trans*-1-phenyl-1-propene was the fastest (3 min), the reduction of iodobenzene the slowest (40 min), while chlorobenzene and bromobenzene were reduced respectively in 6 and 14 min. When iodobenzene and *trans*-1-phenyl-1-propene were reacted competitively, the reduction of *trans*-1-phenyl-1-propene was delayed and iodobenzene reacted first (Figure 1a). The same competitive reaction was carried out with bromobenzene versus *trans*-1-phenyl-1-propene (Figure 1b). In this case, no selectivity was observed. The olefin reduction and the bromobenzene hydrogenolysis took place simultaneously. When chlorobenzene and *trans*-1-phenyl-1-propene were reacted competitively, the olefin was first and selectively reduced (Figure 1c).

These experiments clearly show that the selective removal of a halogen is extremely dependent on the halogen. When the hydrogenolysis was carried out separately, the speed of removal of halogens increased with increasing electronegativity. Chlorine was removed faster than bromine and bromine faster than iodine. When the reaction was carried out in the presence of an easily reducible substrate (*trans*-1-phenyl-1-propene), the less reactive iodobenzene was selectively reduced. Selectivity was obtained only in the case of the iodo compound. As we have recently demonstrated, the selectivity can be explained by a marked adsorption of the aryl iodide on the catalyst.

To investigate the synthetic utility of this reaction, iodine was selectively removed from substrates bearing a benzophenone or an azido moiety. It is well-known that these two groups are easily reduced by Pd and molecular hydrogen.[3]

Benzophenone compounds: The high-yielding hydrogenolysis of **1a** and **1b** show that the position of the iodine atom on the aromatic ring has no influence (Table 1). Even in the presence of other easily reducible functions

(1) (a) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466−1478. (b) Carreño, M. C.; Ruano, J. L. G.; Urbano, A.; Remor, C. Z.; Arroyo, Y. *J. Org. Chem.* **2000**, *65*, 453−458. (c) Saito, S.; Nakagawa, S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 3975−3978. (d) Shibata, I.; Moriuchi-Kawagami, T.; Tanizawa, D.; Suwa, T.; Sugiyama, E.; Matsuda, H.; Baba, A. *J. Org. Chem.* **1998**, *63*, 383−385. (e) Yasuda, M.; Hayashi, K.; Katoh, Y.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **1998**, *120*, 715−721. (f) Ohkuma, T.; Ooka; H.; Ikariya, T.; Noyori, R.; *J. Am. Chem. Soc.* **1995**, *117*, 10417−10418. (g)Yanagisawa, A.; Inoue, H.; Morodome, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10356−10357.

(2) Ambroise, Y.; Mioskowski, C.; Djéga-Mariadassou, G.; Rousseau, B. *J. Org. Chem.* **2000**, *65*, 7183−7186.

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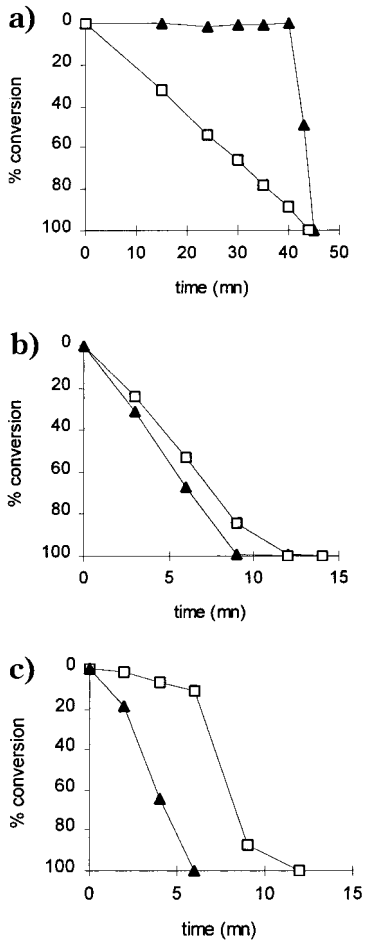


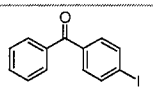
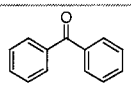
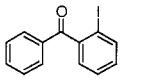
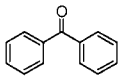
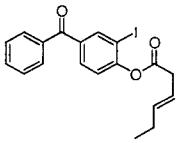
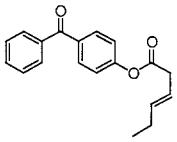
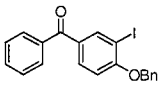
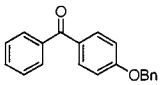
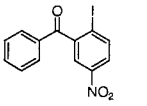
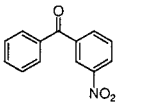
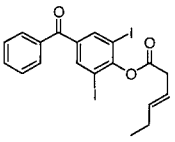
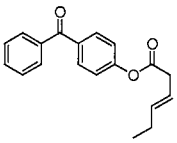
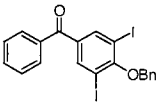
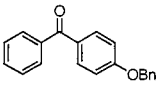
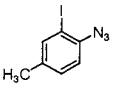
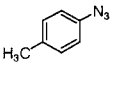
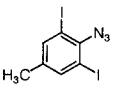
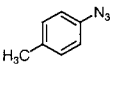
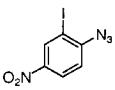
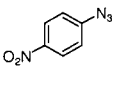
Figure 1. Competitive hydrogenation of halogenobenzene and *trans*-1-phenyl-1-propene with hydrogen and Pd/C catalyst. (a) Reaction between PhI (□) and *trans*-1-phenyl-1-propene (▲). (b) Reaction between PhBr (□) and *trans*-1-phenyl-1-propene (▲). (c) Reaction between PhCl (□) and *trans*-1-phenyl-1-propene (▲).

(double bond, *O*-benzyl, nitro), iodinated benzophenone is cleanly hydrogenolyzed (**1c**−**e**). Diiodo compounds **1f** and **1g** are easily converted to their deiodinated analogues.

Azido compounds: *o*-, *m*-, and *p*-azidoiodobenzenes are cleanly hydrogenolyzed to furnish the azidobenzene (**1**−**j**). To the best of our knowledge, this is the first report where an azido function survived under conditions of catalytic hydrogenation. Aromatic azido functions bearing an electron-donating group (**1k**,**l**) were transformed in high yield. Diiodo analogue **1m** was reduced to furnish azidotoluene in 90% yield. Azido compound **1n** bearing an electron-withdrawing group was reduced in modest yield (60%). It should be noted that an electron-withdrawing group also affects the yield in the benzophenone series where the smallest yield was obtained with nitro compound **1e**.

Deuterium and Tritium Labeling. Azido and benzophenone groups are used for photoaffinity labeling and cross-linking experiments.[4] For the detection of a biological target, photolabeling reagents must be available in an isotopically labeled form. To label these compounds,

Table 1. Hydrogenolysis of Iodobenzophenone and Iodoaryl Azide

	Substrate		Product	Yield %	Time min
1a		**2a**		99	120
1b		**2b**		99	70
1c		**2c**		> 95	45
1d		**2d**		95	90
1e		**2e**		80	150
1f		**2f**		> 95	180
1g		**2g**		95	150
1h		**2h**		95	100
1i		**2i**		95	60
1j		**2j**		95	75
1k		**2k**		95	300
1l		**2l**		95	45
1m		**2m**		90	75
1n		**2n**		60	30

(3) (a) Marques, C. A.; Selva, M.; Tundo, P. *J. Org. Chem.* **1995**, *60*, 2430−2435. (b) Novak, M.; Kahley, M. J.; Lin, J.; Kennedy, S. A.; James, T. G. *J. Org. Chem.* **1995**, *60*, 8294−8304. (c) Gunda, G.; Liu, Y.; Boge, T. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*(14), 1829−1832. (d) Heier, R. F.; Dolak, L. A.; Duncan, J. N.; Hyslop, D. K.; Lipton, M. F.; Martin, I. J.; Mauragis, M. A.; Piercey, M. F.; Nichols, N. F.; Schreur, P. J. K. D.; Smith, M. W.; Moon, M. W. *J. Med. Chem.* **1997**, *40*(5), 639−646.

(4) (a) Hori, N.; Iwai, S.; Inoue, H.; Ohtsuka, E. *J. Biol. Chem.* **1992**, *267*, 15591−15594. (b) Brunner, J. *Annu. Rev. Biochem.* **1993**, *62*, 483−514. (c) Delfino, J. M.; Schreiber, S. L.; Richards, F. M. *J. Am. Chem. Soc.* **1993**, *115*, 3458−3474. (d) Kotzyba-Hibert, F.; Kapfer, I.; Goeldner, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1296−1312. (e) Fleming, S. A. *Tetrahedron*, **1995**, *46*, 12479−12520. (f) Grassi, D.; Lippuner, V.; Aebi, M.; Brunner, J.; Vasella, A. *J. Am. Chem. Soc.* **1997**, *119*, 10992−10999. (g) Hatanaka, Y.; Hashimoto, M.; Kanaoka, Y. *J. Am. Chem. Soc.* **1998**, *120*, 453−454.

Table 2. Deuterium and Tritium Labeling

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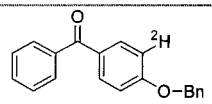
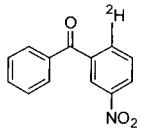
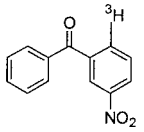
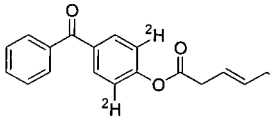
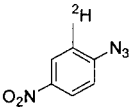
3		98%
4		94%
5		91% (26 Ci/mmole)
6		90%
7		95%

we used the hydrodeiodination reaction and replaced hydrogen by deuterium or tritium. As shown in Table 2, the isotopic enrichment was close to the theoretical maximum, indicating that the method is particularly well suited to the problem of isotopic labeling.

These are simple models that highlight an application in the synthesis of deuterium- or tritium-labeled compounds. Using this approach, we recently reported the tritium labeling of a photosensitive transmembrane probe.[5] This probe allows the determination of the center of the transmembrane domain of glycophorin A in a membrane by selective functionalization of the protein within a phospholipid bilayer.

Conclusion

We have shown that the speed of removal of halogen increases with increasing electronegativity I < Br < Cl. Nevertheless, selective dehydrohalogenation in compounds containing other reducible functions can be achieved only with iodine and not with bromine or chlorine. Selective deiodination of iodobenzophenone could be accomplished without reducing the carbonyl group. We have demonstrated that hydrogenolysis of azidoiodoaromatic compounds to the corresponding azido compounds is high yielding. We took advantage of this selectivity to label benzophenone- and azido-containing compounds by deuterium and tritium.

Experimental Section

General Remarks. Deuterium gas was from Eurisotop (France) and contained 99% deuterium. Tritium gas was from CEA (France) and contained 98.9% tritium, 0.7% deuterium, and 0.4% hydrogen. The 10% Pd/C was from Aldrich (catalog no. 20,569-9). Thin-layer chromatography was run using precoated silica gel plates (Merck, 0.25 mm). Chromatography separations were performed on Merck silica gel 60 (230−400 mesh). The radio-TLC plates were analyzed using a Radiomatic RTLC scanner. Scintillation counting was carried out with a Wallac 1409 apparatus using a "mélange scintillant III" cocktail from SDS. ^{1}H, ^{13}C, and ^{3}H NMR spectra were recorded at 300, 75, and 320 MHz. Chemical shifts were measured in parts per million relative to the residual proton signal from the deuterated solvent of acetone-d_6 at δ 2.04 ppm (^{1}H) and 206.0 ppm (^{13}C), $CDCl_3$ δ 7.24 ppm (^{1}H) and 77.0 ppm (^{13}C), D_2O δ 4.80 ppm (^{1}H), methanol-d_4 δ 3.30 ppm (^{1}H) and 49.0 ppm (^{13}C). Mass spectra were determined by methane or ammoniac ionization techniques or by electronic ionization at 70 eV. High-resolution mass spectra were recorded by LSIMS (with Cs^+).

General Procedure for the Hydrogenation. 2-Iodo-5-nitrobenzophenone **5** (26.8 mg, 76 μmol) was dissolved in MeOH (10 mL) and triethylamine (100 μL, 10 equiv). Pd/C (7.5 mg, 0.1 equiv) and cumene as internal standard (50.3 mg) were added. The reaction mixture was vigorously stirred at 20 °C under 1 atm of hydrogen. During the reaction, the pressure of H_2 was maintained constant by a continuous supply of H_2 (checked with an accurate manometer). Aliquots (80 μL) were sampled at 0, 5, 20, 40, 60, 90, 120, 150, 180, and 240 min, filtered, and analyzed by HPLC (H_2O/MeCN = 1/1, 1 mL/min, UV detection at 220 nm). The rates of conversion of **5** and production of 5-nitro-benzophenone were derived from the respective areas by correlation with internal standard.

This typical procedure was applied for all the hydrogenations described in this paper except for compounds **1c**, **1f**, and **1g**. For compounds **1c** and **1f**, triethylamine was replaced by DABCO in order to avoid saponification. For hydrogenation of compound **1g** methanol was replaced by a mixture of CH_2Cl_2 (50%) and methanol (50%).

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0109669

(5) Ogawa, Y.; Hahn, W.; Garnier, P.; Higashi, N.; Massotte, D.; Metz-Boutigue, M. H.; Rousseau, B.; Sunamoto, J.; Ourisson, G.; Nakatani, Y. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*(5), 945−946.