

The First Efficient Iodination of Unactivated Aliphatic Hydrocarbons**

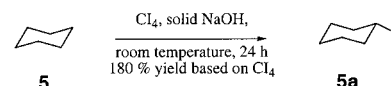
Peter R. Schreiner,* Oliver Lauenstein, Ekaterina D. Butova, and Andrey A. Fokin*

Dedicated to Professor Armin de Meijere on the occasion of his 60th birthday

The selective and efficient manipulation of unreactive C–H bonds in aliphatic hydrocarbons is particularly difficult and is, despite extensive research efforts, one of the major challenges in chemistry.^[1–3] Activation per se is not so much of a problem, as carbenes,^[4] superacids,^[1, 5, 6] and highly reactive free radicals^[7] readily cleave alkane C–H and C–C bonds. However, many of these reactions show low selectivities and often lead to skeletal isomerizations as well as to oligomerizations.^[6] Considerable progress has been made in the selective activation and derivatization of aliphatic hydrocarbons by utilizing enzymatic processes^[7] and electronically unsaturated transition metal complexes.^[8–10] A major drawback of these reactions is their inability to lend themselves to large-scale production which limits their general applicability. We now report on an efficient and synthetically relevant method for the iodination of aliphatic hydrocarbons.^[11]

Radical halogenations probably are the simplest way to functionalize hydrocarbons because they only require a radical chain initiator, light, or higher temperatures.^[2] The direct free-radical halogenation of aliphatic hydrocarbons with iodine, in contrast to the other halogens, is about 20–30 kcal mol^{–1} endothermic and does not allow a chain reaction to occur.^[12–14] To date, there is no preparative method to produce iodoalkanes *directly* from aliphatic compounds.^[12, 13, 15, 16] In our efforts to develop new hydrocarbon activation methods, we recently reported on the bromination of alkanes with CBr₄ under phase-transfer (PT) catalytic conditions by employing alkanes over highly concentrated aqueous solutions of sodium hydroxide.^[17] The mechanistic evidence suggests that these reactions are initiated by reduction of CBr₄,^[18, 19] subsequently leading to the tribromomethyl radical, •CBr₃ (identified as a trapping product with a radical scavenger),^[18] which abstracts H• from RH to produce bromoform and alkyl radicals R•. These react with CBr₄ to afford the desired alkyl bromide and a new •CBr₃ radical.

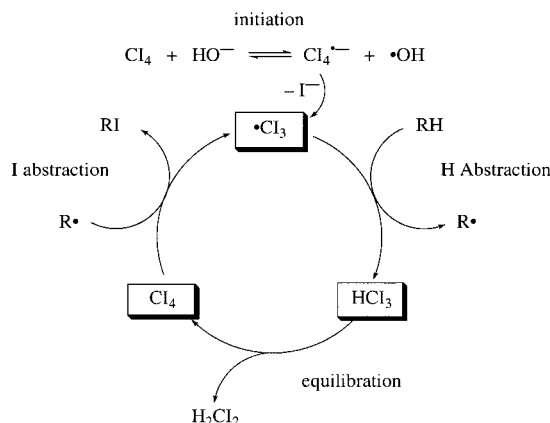
This method is not directly applicable to iodinations because water may hydrolyze Cl₄ and the desired iodoalkanes, which are generally more labile (though the solubilities in water are generally low) than the corresponding alkyl bromides. This also made the use of quaternary ammonium salts as phase-transfer catalysts, which are deactivated in the presence of iodide, unnecessary.^[20] With the resulting new experimental protocol involving a homogeneous liquid over a solid phase, we found that cyclohexane (**5**) could be iodinated cleanly (Scheme 1) in the presence of powdered NaOH in 180 % yield (based on Cl₄ since cyclohexane also serves as the solvent).



Scheme 1. Iodination of cyclohexane (**5**)

The fact that more than one iodine atom is transferred from the initial Cl₄ indicated that this species must be regenerated from iodoform during the reaction, unless the latter were to react directly in a similar fashion with hydrocarbons. Hence, we examined whether Cl₄ is formed by equilibration of iodoform dissolved in CH₂Cl₂ over solid NaOH; similar equilibria are known for other polyhalomethanes.^[21, 22] The identification of Cl₄ is difficult because its ¹³C NMR signal at $\delta = -292$ is strongly broadened.^[23] Both Raman and infrared intensities are very weak due to the high symmetry (*T_d*) and are not distinct from other polyhalomethane absorptions; UV spectroscopy is similarly unsuitable. We eventually succeeded in identifying Cl₄ in the {2 HCl₃ $\rightleftharpoons$ H₂Cl₂ + Cl₄} equilibration in either direction by low-energy electron-impact (EI) mass spectrometry. Diiodomethylene could be clearly identified by NMR spectroscopy in this specific equilibrium and in all iodinations described in the present work.

This finding suggested the use of the more stable and much cheaper iodoform instead of Cl₄ which would then be generated in situ (Scheme 2). In contrast to other haloforms, iodoform reluctantly gives diiodocarbene which may insert into C–H bonds under PT conditions; dihalocarbene side



Scheme 2. Mechanistic hypothesis for the iodination of aliphatic hydrocarbons under basic conditions. The R• radical produced in the initiation steps react with Cl₄ to give the desired iodoalkane and the more selective •Cl₃ radical which carries the chain further. Equilibration of iodoform regenerates Cl₄.

[*] Dr. P. R. Schreiner, Dipl.-Chem. O. Lauenstein
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: (+49) 551-399475
E-mail: pschrei@gwdg.de

Prof. Dr. A. A. Fokin, Dr. E. D. Butova
Department of Organic Chemistry, Kiev Polytechnic Institute
pr. Pobedy, 37, 252056 Kiev (Ukraine)
Fax: (+38) 044-2742004
E-mail: aaf@xtf.ntu-kpi.ua

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reactions are negligible under our reaction conditions.^[24] As our working mechanism in Scheme 1 suggests,^[17, 18] the radical chain carrier is the triiodomethyl radical ($\cdot\text{CI}_3$) which is generated in the initial steps of the reaction in low concentrations, preventing polyiodination and other typical radical side reactions.

The iodination protocol is quite generally applicable (Table 1): when treated with iodoform in the presence of solid NaOH, straight chain (**1–3**), cyclic (**4–6**), acyclic branched (**7–9**), and cage (**10** and **11**) alkanes can be transformed into their corresponding alkyl monoiodides. Even the extremely unreactive *n*-alkanes **1–3** can be converted preparatively to their corresponding alkyl iodides; no *n*-alkane derived side products were detected by proton or carbon NMR spectroscopy. In some cases the yields can be improved either at higher temperatures or with longer reaction times if the resulting alkyl iodide is sufficiently stable. The yield increase of 1-iodocycloheptane **6a** to 73% at 105 °C is an illustrative example. Simple filtration of solid NaOH, removal of excess

hydrocarbon and distillation yields the monoiodide in pure form. Hence, the application of this method is quite practical and can be easily conducted on large scale.

Only secondary and tertiary positions are attacked in our halogenation processes. While secondary iodoalkanes are stable (no elimination or other side reactions were detected in preparative mass-balanced reactions; apart from the products only hydrocarbon starting materials were recovered with a mass loss of <5% for the overall reaction), some tertiary products are prone to elimination under the basic reaction conditions. For instance, the branched hydrocarbons **7–9** give no or little tertiary alkyl iodides and low yields of secondary products. Independent experiments show that **5a** is stable under our reaction conditions, while **7a** is not (elimination). Only mixtures of secondary iodides but no tertiary iodide could be detected (NMR spectroscopy) in the reactions of methylcyclohexane. Hence, 1-iodoadamantane could be isolated in high yield simply because it cannot eliminate.

Table 1. The reactions of some aliphatic hydrocarbons with HCl_3 in the presence of solid NaOH. Preparative yields^[a] and isomer ratio (NMR) in parentheses.

Substrate	Cond. ^[b]	<i>T</i> [°C]	<i>t</i> [h]	Products
 1	A ^[c]	25	24	 1a (32)
 2	A	25	24	 2a  2b (76, 4:1)
 3	A	25	24	 3a  3b (83, 1.5:1)
 4	A	25	16	 4a (92)
 5	A	25	24	 5a (75)
 6	A	25	96	 6a (39)
6	A ^[c]	105	36	6a (73)
 7	A ^[c]	25	72	 7a (traces)
 8	A	25	48	 8a (traces)  8b (27)
 9	A	25	48	 9a (traces)  9b (16)
 10	B	25	48	 10a  10b (42, 5:1)
 11	B	25	96	 11a (53) ^[d]  11b (5) ^[d]

[a] Yield relative to HCl_3 used. [b] Procedure A for liquid alkanes at room temperature; procedure B for solutions in CH_2Cl_2 .^[24] [c] Soluble in a pressure vessel. [d] Yield relative to the starting hydrocarbon after purification by column chromatography.

In summary, we have found the first *preparative* method for direct iodination of hydrocarbons. The procedure is simple yet efficient and even normally completely unreactive straight chain alkanes can be iodinated easily. Further developments of this method are likely to find application in the widely used biochemical radioiodination^[25] techniques and in the production of specialty chemicals for the pharmaceutical industry. Elaborate mechanistic studies are well underway in our laboratories.

Experimental Section

Representative preparative procedure for liquid and solid hydrocarbons: a) Iodocyclohexane (**5a**): Powdered NaOH (10.0 g) and iodoform (7.0 g, 17.8 mmol) were added to cyclohexane (100 mL). The solution was stirred for 24 h at room temperature. The organic phase was separated from the solid phase by filtration; vacuum distillation gave pure **5a** (2.8 g, 13.4 mmol, 75% relative to HCl₃). b) 1-Iodoadamantane (**11a**): Solid NaOH (2.4 g) was added to a solution of iodoform (0.79 g, 2.0 mmol), CH₂Cl₂ (20 mL), and substrate (0.27 g, 2.0 mmol). The solution was stirred for 96 h. The organic phase was separated from the solid phase by filtration, and the solid phase was washed with CH₂Cl₂ (3 × 20 mL); volatile components were removed by vacuum distillation. The products were purified by column chromatography (silica gel, petroleum ether, b.p. < 60 °C, *R_f* (**11a**) = 0.48; *R_f* (**11b**) = 0.25) to give 1-iodoadamantane (**11a**) (0.28 g, 1.1 mmol, 53%) and 1,3-diiodoadamantane (**11b**) (0.04 g, 0.1 mmol, 5%). All products were identified by GC, MS, and NMR analysis and were found to be identical to standard samples. Preparative yields are given in Table 1. Complete mass balances were determined for cyclohexane and adamantane.

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- [1] G. A. Olah, A. Molnár, *Hydrocarbon Chemistry*, Wiley, New York, **1995**.
- [2] C. L. Hill, *Activation and Functionalization of Alkanes*, Wiley, New York, **1989**.
- [3] J. A. Davies, P. L. Watson, J. F. Liebman, A. Greenberg, *Selective Hydrocarbon Activation, Principles and Progress*, VCH, Weinheim, **1990**.
- [4] M. Jones, R. A. Moss, *Carbenes*, Wiley, New York, **1973**.
- [5] G. A. Olah, O. Farooq, G. K. S. Prakash, *Activation and Functionalization of Alkanes*, Wiley, New York, **1989**.
- [6] J. Sommer, J. Bukala, *Acc. Chem. Res.* **1993**, *26*, 370–376.
- [7] P. A. Frey, *Chem. Rev.* **1990**, *90*, 1343–1357.
- [8] R. H. Crabtree, *Chem. Rev.* **1995**, *95*, 987–1007.
- [9] B. A. Arndtsen, R. G. Bergman, *Science* **1995**, *270*, 1970–1973.
- [10] S. E. Bromberg, W. Yang, M. C. Asplund, T. Lian, B. K. McNamara, K. T. Kotz, J. S. Yeston, M. Wilkens, H. Frei, R. G. Bergman, C. B. Harris, *Science* **1997**, *278*, 260–263.
- [11] P. R. Schreiner, A. A. Fokin, O. Lauenstein, E. D. Butova, patent pending.
- [12] L. Liguori, H.-R. Bjørsvik, A. Bravo, R. Fontana, F. Minisci, *Chem. Commun.* **1997**, 1501–1502.
- [13] D. D. Tanner, G. C. Gidley, *J. Am. Chem. Soc.* **1968**, *90*, 808–809.
- [14] D. D. Tanner, J. R. Rowe, A. Potter, *J. Org. Chem.* **1986**, *51*, 457–460.
- [15] G. A. Olah, Q. Wang, G. Sandford, G. K. S. Prakash, *J. Org. Chem.* **1993**, *58*, 3194–3195.
- [16] "Formation of carbon-halogen bonds (Cl, Br, I)": Y. Sasson in *The Chemistry of functional groups, Supplement D2* (Eds.: S. Patai, Z. Rappoport), Wiley, Chichester, **1995**, pp. 535–628.
- [17] P. R. Schreiner, O. Lauenstein, I. V. Kolomitsyn, S. Nadi, A. A. Fokin, *Angew. Chem.* **1998**, *110*, 1993–1995; *Angew. Chem. Int. Ed.* **1998**, *37*,

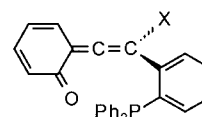
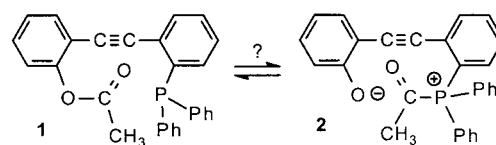
1895–1897; see also: *Nachr. Chem. Tech. Lab.* **1998**, *46*, 706; *Chem. Eng. News* **1998**, 76(28), 55.

- [18] P. R. Schreiner, O. Lauenstein, A. A. Fokin, unpublished results.
- [19] D. T. Sawyer, J. L. Roberts, *Acc. Chem. Res.* **1988**, *21*, 469–476.
- [20] R. Mathias, P. Weyerstahl, *Angew. Chem.* **1974**, *86*, 42–44; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 132–133.
- [21] E. V. Dehmlow, M. Lissel, *Chem. Ber.* **1978**, *111*, 3873–3878.
- [22] J. A. Orvik, *J. Org. Chem.* **1996**, *61*, 4933–4936.
- [23] E. Breitmaier, W. Voelter, *Carbon-13 NMR Spectroscopy*, VCH, Weinheim, **1990**.
- [24] E. V. Dehmlow, S. S. Dehmlow, *Phase-Transfer Catalysis*, VCH, Weinheim, **1993**.
- [25] R. H. Seevers, R. E. Counsell, *Chem. Rev.* **1982**, *82*, 575–590.

Unusual Oxaphosphoranes by Acyl Transfer from *o*-Acetoxy-*o*'-diphenylphosphanyltolane**

Edwin Vedejs* and Peter L. Steck

As part of a study on phosphane-catalyzed acylations,^[1] we were interested in the chemistry of the *o*,*o*'-disubstituted tolane **1**. The linear acetylene linker provides for close proximity between the phosphorus atom and the carbonyl group,^[2] perhaps sufficient to promote bonding interactions



3a, X = C(O)CH₃

3b, X = H

that would lead to the P-acyl derivative **2** by intramolecular acyl transfer. In its zwitterionic resonance form, **2** is formally analogous to the *P*-acylphosphonium carboxylate ion pair that is the reactive intermediate in the acylation of phosphanes with anhydrides.^[1a] If **1** is capable of O to P acyl transfer, then **2** might function as an acyl donor towards external nucleophiles and could also serve as a geometrically restricted mechanistic analogue of *P*-acylphosphonium car-

[*] Prof. E. Vedejs,^[+] P. L. Steck
Chemistry Department, University of Wisconsin
Madison, WI 53706

[+] Current address:
Department of Chemistry, University of Michigan
Ann Arbor, MI 48109
Fax: (+1) 734-615-1628
E-mail: edved@umich.edu

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