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Direct Iodination of Alkanes

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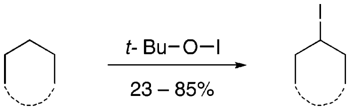
ABSTRACT

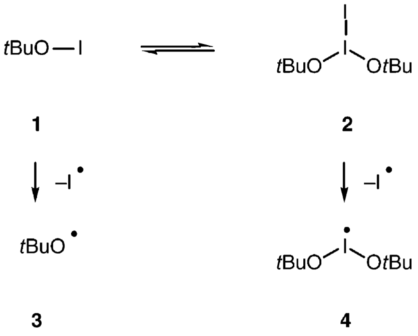


A cheap and efficient iodination of hydrocarbons can be achieved by generating *tert*-butyl hypoiodite from iodine and sodium *tert*-butoxide. The alkane is reactant and solvent, and this metal-free process provides a clean solution for their direct iodination.

The activation of carbon−hydrogen bonds in aliphatic hydrocarbons is difficult to achieve and a challenging process in organic synthesis. Hydrocarbons cannot be used in synthetic chemistry without prior activation, and as crude oil is a mixture of various hydrocarbons, they are readily available and extremely cheap starting materials. There are several known methods for the activation of hydrocarbons, but either the activation method is very strong and unselective (e.g., carbenes, superacids, highly reactive free radicals[1]) and can lead to skeletal rearrangements and oligomerizations,[2] or the method involves toxic or expensive transition-metal catalysts.[3] The search for new and efficient hydrocarbon activation methods is therefore continuing. One-electron transfer processes like radical chain reactions are operating in many alkane oxidations and are a simple way for their functionalization. Radical halogenations require only a radical chain initiator like light or higher temperatures. In contrast to other halogens, the direct free radical halogenation of alkanes with iodine is endothermic and the chain reaction will not proceed. The iodination of alkanes is, therefore, particularly challenging. *tert*-Butyl hypochlorite[4] and *tert*-butyl hypobromite[5] are known reagents for the chlorination and bromination of alkanes. *tert*-Butyl hypoiodite for iodinations of unfunctionalized hydrocarbons has been reported earlier,[6] and the same reagent might be involved also in a recent procedure using a mixture of (bisacetoxy)iodobenzene, iodine, and *tert*-butyl alcohol.[7] Other reagents for iodinations of alkanes have been reported as well.[8−10]

We describe here an in situ generation of *tert*-butyl hypoiodite for an efficient iodination of various alkanes (Scheme 1). Different protocols for the synthesis of *tert*-butyl hypoiodite have been reported which result in compounds having different reactivities.[11] Hence, there is some uncertainty as to the structure of *tert*-butyl hypoiodite **1**. Molecular weight measurements have suggested an equilibrium between **1** and the λ^3-iodane **2**.[11] Other methods for the preparation of *tert*-butyl hypoiodite involve the reaction of *tert*-butyl hypochlorite with iodine or with metal iodides (HgI_2, AgI).[6] The structure of the hydrogen-abstracting species might therefore be the iodonyl radical **4** or the well-known oxygen-centered radical **3**, which might also be generated from **4** by cleavage into **3** and **1**.[12] Iodine (III) radicals are known to be hydrogen abstracting species.[13] The

Scheme 1. Radicals Derived from *tert*-butylhypoiodite.



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(5) Walling, C.; Padwa, A. *J. Org. Chem.* **1962**, *27*, 2976.
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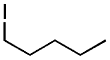
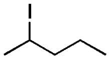
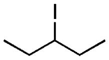
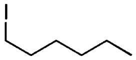
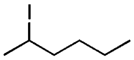
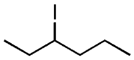
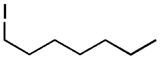
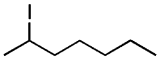
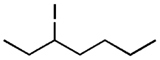
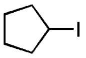
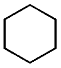
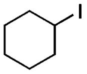
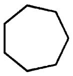
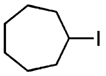
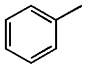
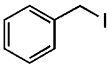
Table 1. Iodination of Alkanes Using *tert*-Butyl Hypoiodite at 40 °C

Entry	Substrate	Products			Yield[a]
1	 **5**	 **5a**	 **5b**	 **5c**	61% (1:1:2)
2					75% (1:3:2)[b]
3	 **6**	 **6a**	 **6b**	 **6c**	50% (1:3:2)
4	 **7**	 **7a**	 **7b**	 **7c**	35% (1:2.5:3.4)[c]
5	 **8**	 **8a**			85%
6	 **9**	 **9a**			84%
7	 **10**	 **10a**			23%
8	 **11**	 **11a**			50%

[a] Isolated yields, isomeric ratios determined by NMR. [b] A mixture of 1 equiv of Br_2, 1 equiv of I_2, and 2 equiv of *t*-BuONa was used, and only iodopentane was formed. [c] No 4-iodoheptane was detected.

weak oxygen−iodine bond in **1** can be cleaved photochemically or thermally to afford the *tert*-butoxy radical **3**. The fragmentation of the *tert*-butoxy radical **3** into acetone and a methyl radical is also known but this does not compete with the fast abstraction of hydrogen atoms by **3** from alkanes.[14] We adopted the most simple protocol for the generation of *tert*-butyl hypoiodite, the reaction between sodium *tert*-butoxide and iodine.[15] The generation of *tert*-butyl hypoiodite is performed in an excess of the alkane (concentration: 0.05−0.1 m). The alkane is then iodinated under very mild reaction conditions at 40 °C for several hours. The hydrogen-abstracting radical **3** or **4** is formed by thermal decomposition of the precursor **1**/**2** at this temperature. The alkyl radical then abstracts an iodine atom from **1**/**2** or recombines with an iodine radical to form the iodoalkanes. Even extremely unreactive *n*-alkanes (**5**−**7**) can be converted into the corresponding alkyl iodides and the products can be separated from excess alkane and purified by simple distillation. The yields obtained using this method of an in situ generation of *tert*-butyl hypoiodite **1** are higher than using other methods. When **1** is synthesized from *tert*-butyl hypochlorite and HgI_2, cyclohexane is iodinated in 51% yield using 1,1,2-trichlorotrifluoroethane (Freon 113) as solvent (iodination of toluene: 34%). These reactions were only carried out on a 1 mmol scale under photochemical conditions.[6,11] By our method of *in-situ* generation of **1** we obtain iodocyclohexane in 85% and benzyliodide in 50% yield on a 20 mmol scale (Table 1, entries 6 and 8).[16]

Different metal alkoxides, such as sodium methoxide, sodium ethoxide, potassium *tert*-butoxide, and sodium

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(16) **Representative Procedure.** Iodocyclohexane **9a**: Iodine (5.08 g, 20 mmol) was dissolved in cyclohexane (220 mL, 2 mol), and sodium *tert*-butoxide (1.92 g, 20 mmol) was added. The suspension was stirred at 40 °C for 15 h. The mixture was washed with 0.2% aq $Na_2S_2O_3$ (60 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue distilled to yield iodocyclohexane **9a** (3.55 g, 84%) as a colorless liquid. All reaction products were identified by GC/MS and NMR analysis and were found to be identical to published data.

3-ethyl-3-pentoxide, were used for the formation of hypoiodites, but sodium *tert*-butoxide was found to form the most efficient hypoiodite for the iodination of alkanes. A 1:1 ratio of sodium *tert*-butoxide and iodine is optimal for the iodination as an excess of sodium *tert*-butoxide can lead to elimination, whereas iodine in excess might behave as a radical scavenger. Other sources of iodine have been investigated as well, but iodine monochloride or *N*-iodosuccinimide are inefficient reagents for the preparation of *tert*-butyl hypoiodite.

Interestingly, a combination of bromine and iodine generates a mixture of *tert*-butyl hypobromite and *tert*-butyl hypoiodite, but only the iodoalkane was detected as a product in higher yields (Table 1, entry 2). This can be due to the formation of a λ^3-bromane which might result in a different hydrogen-abstracting radical. The selectivity of the hydrogen abstraction (primary/secondary) is at about 1:5 (Table 1, entries 1 and 2). A similar preference for secondary hydrogen atoms is also observed using hexane (Table 1, entry 3) or heptane (Table 1, entry 4) with selectivities of about 1:7 or 1:10 (per hydrogen), respectively. These are lower selectivities than observed in the photochemically initiated reactions with **1** generated from *tert*-butyl hypochlorite and HgI_2 (1:15−1:29) which indicates a smaller contribution from radical **4** in the reaction described herein, as the selectivity for *tert*-butoxy radicals **3** was determined to be about 1:8 (primary:secondary) in the iodination of *n*-butane.[4] Reactions of alkanes with tertiary C−H bonds (3-methylpentane) have been without success, because the resulting iodoalkanes seem to be highly instable under the reaction conditions and could not be isolated.

When a mixture of pentane and an additional solvent (THF, Et_2O, MeOH, CH_2Cl_2) is employed in the reaction described above, no iodopentane is formed but *n*-decane can be isolated in high yields. The same reaction is possible with a mixture of *tert*-butyl peroxide and iodine leading to a quantitative formation of *n*-decane.[17] The dimerization was achieved with acyclic alkanes but cyclic alkanes did not undergo this reaction.[18]

In conclusion, we have developed a metal-free process for iodination of alkanes using *tert*-butyl hypoiodite as a cheap and efficient reagent. The procedure is very simple and can be done without prior purification of the reagents. Further developments might find application in the production of fine chemicals for the pharmaceutical industry.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] The reaction of pentane with $(t\text{-BuO})_2$ alone results also in the formation of *n*-decane although with a much lower yield (25%).

[18] There are only a few reports on mercury- and silver-photosensitized dimerizations of alkanes: (a) Ozin, G. A.; Hugues, F. *J. Phys. Chem.* **1982**, *86*, 5174. (b) Brown, S. H.; Crabtree, R. H. *J. Am. Chem. Soc.* **1989**, *111*, 2935. (c) Brown, S. H.; Crabtree, R. H. *J. Am. Chem. Soc.* **1989**, *111*, 2946.