C–H Activation

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New Iodination Reactions of Saturated Hydrocarbons[**]

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Selective processes that afford functionalized derivatives from the reaction of nonactivated C–H bonds are of current interest.[1] Bromination and chlorination reactions are valuable tools for this purpose with saturated hydrocarbons.[2] However, the related iodination is not so well developed.[3] Herein, we report on new iodination reactions of alkanes under mild thermal conditions. The process relies on the use of the combination of hypervalent iodine, I_2, and trimethylsilyl azide ($TMSN_3$). Furthermore, a related and efficient iodination in water, using H_2O_2 as a convenient source for the oxidant, has also been established.

Hydrocarbons can be iodinated under photochemical conditions by employing $PhI(OAc)_2/I_2/t$BuOH, a process that likely involves the formation of intermediate alkoxyl radicals.[3e] Alternative processes that lead to the development of

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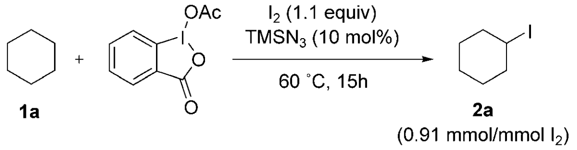
Supporting information for this article (^{13}C NMR spectra of compounds **2a–k**) is available on the WWW under http://www.angewandte.org or from the author.

new methodology and involve different types of intermediates as the species responsible for the C–H activation step are of great significance and, overall, might result in new and distinctive synthetic features. Being interested in employing more convenient thermal conditions, we decided to investigate reactions using azide to activate the hypervalent iodine reagent.[4] 1-Acetoxy-1,2-benziodoxole-3(1*H*)-one[5] was chosen as the hypervalent iodine reagent. We expected that a catalytic amount of azide would be able to promote the desired iodination. This assumption was initially validated with cyclohexane (**1a**) as model compound, using $TMSN_3$ as the azide donor (Scheme 1).

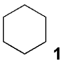
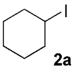
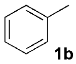
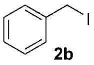
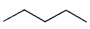
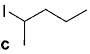
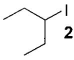
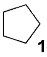
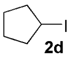
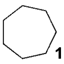
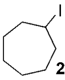
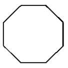
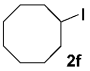
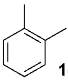
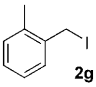
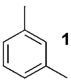
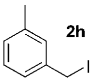
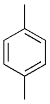
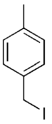
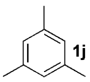
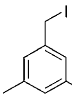
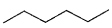
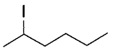
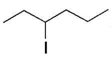


Scheme 1. Synthesis of iodocyclohexane **2a** from the thermal reaction of cyclohexane (**1a**) with I_2 promoted by a cyclic λ^3-iodane and catalytic amounts of $TMSN_3$ (Method A, Table 1).

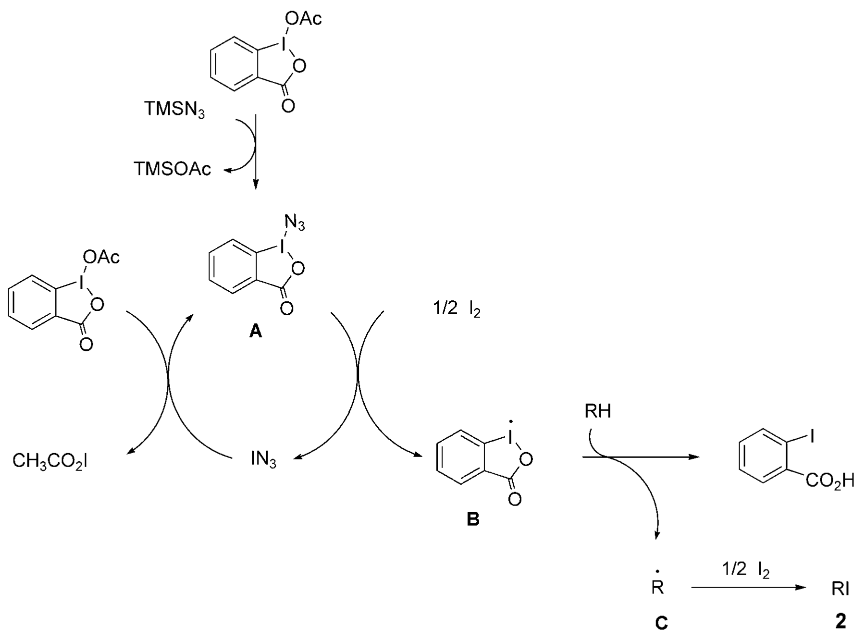
The concentration of the azide is crucial to accomplish the reported iodination. Routinely, to investigate the scope of the iodination (method A),[6] 4×10^{-3} M of azide was used. The results are summarized in Table 1. This novel iodination can be applied to different alkanes, either cyclic or acyclic. Interestingly, for the latter, an improved selectivity is noted.[3e] Now, only secondary positions are iodinated, without significant evidence for related functionalization of the primary ones. Benzylic positions are equally cleanly iodinated. This new reaction provides useful indicators. It relies on a thermal process; moreover, the use of a catalytic amount of azide and the observed selectivity for the iodination of linear hydrocarbons are also significant. Furthermore, this new process is very convenient with regard to the isolation of **2**, as well as the recovery of the reaction by-product. *o*-Iodobenzoic acid can be easily removed and recycled by simple aqueous extraction at proper pH. For the iodination of xylenes, an additional feature is noted. These are very efficient processes, which give rise to an increase in the incorporation of iodine atoms into the organic structure. Now, under proper conditions, most of the I_2 can be successfully used to functionalize the hydrocarbon.[7] On the basis of the formed products, the well-documented chemistry of azidobenziodoxoles, and taking into consideration the above-mentioned features, we propose that the sequence in Scheme 2 offers a feasible mechanistic rationalization for the reported iodinations.

Table 1: Thermal iodination of hydrocarbons **1** to give alkyl iodides **2**.

$$\underset{\mathbf{1}}{\text{R-H}} \xrightarrow[\text{oxidant/MN}_3]{\text{I}_2} \underset{\mathbf{2}}{\text{R-I}}$$

Entry	1	Method	*t* [h]	2	Yield[a]
1	 **1a**	A[b] B[c]	15 19	 **2a**	0.91 1.31 (1.43)[d]
2	 **1b**	A B	18 13	 **2b**	0.89 1.88 (1.99)[d]
3	 **1c**	A B	18 8	 **2c**  **2c′**	0.71[e,f] 1.03[e] (1.33)[d]
4	 **1d**	A B	18 6	 **2d**	0.38 (0.90)[f] 1.33 (1.42)[d]
5	 **1e**	A B	30 13	 **2e**	–[g] 1.27
6	 **1f**	A B	56 13	 **2f**	0.58 (0.90)[h] 1.08
7	 **1g**	A B	18 19	 **2g**	1.59 1.18
8	 **1h**	A B	18 19	 **2h**	1.54 1.68
9	 **1i**	A B	18 9	 **2i**	1.58 0.57
10	 **1j**	A B	17 20	 **2j**	0.79 1.46
11	 **1k**	A B	15 18	 **2k**  **2k′**	0.43[i] –[j]

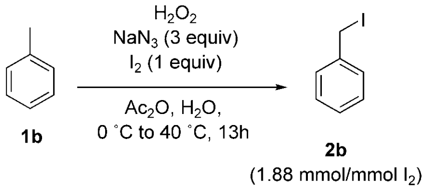
[a] Given as the ratio between mmol of isolated iodinated compound **2** per mmol of added iodine (mmol of **2** per mmol of I_2). [b] See Scheme 1 and reference [6]. [c] See Scheme 3 and reference [15]. [d] In parentheses, yield obtained by integration from the ^{1}H NMR spectra of the crude reaction mixture (1-phenylethanol or anisole were used as an externally added standard to record the NMR spectra). [e] Ratio **2c**:**2c′** ≈ 2.3:1, by ^{1}H NMR spectroscopy (300 MHz) and GC. [f] Using one equivalent of $TMSN_3$ with respect to the iodane. Iodination of **1c** was not observed when 10 mol% of $TMSN_3$ was used. [g] 0.62 mmol of *trans*-1-acetoxy-1-methyl-2-iodocyclohexane were formed. See reference [3e]. [h] Reaction time 20 h, one equivalent of $TMSN_3$ was used. [i] Ratio **2k**:**2k′** ≈ 1:1.1 by GC. [j] Only traces of iodinated derivatives were detected.



Scheme 2. Proposed mechanism for the conversion of **1** into **2** (Method A, Table 1).

First, the starting acetoxyiodane leads to the formation of the known[5b,c] azidoiodane **A**. Next, interaction with I_2 should render active species, such as the iodanyl radical **B**,[8] a process in which a fraction of iodine acts as an efficient scavenger of azido radicals. The radical **B** would be responsible for the activation of the alkane[9] giving rise to *o*-iodobenzoic acid and a C-centered radical **C**, which then furnishes **2**[10] by trapping iodine.[11]

In an attempt to perform related reactions using simpler reagents we have explored the reaction of alkanes with iodine, aqueous solutions of NaN_3,[12] and H_2O_2 as oxidant.[13] We found that, in the presence of acetic anhydride, an efficient iodination reaction takes place, as depicted in Scheme 3 for the functionalization of the benzylic position of toluene. The addition of small amounts of water adjusts the concentration of H_2O_2 and minimizes the formation of by-products (alcohol, acetate).[14]



Scheme 3. Synthesis of α-iodotoluene (**2b**) by a C–H functionalization reaction in water (Method B, Table 1).

This new reaction (see Table 1, method B[15] for data concerning the scope), on average, shows improved efficiency with respect to iodine incorporation into the organic precursor, allows an easy isolation of compounds **2**, and retains the selectivity for the iodination of secondary versus primary positions. Accordingly, linear pentane (**1c**) is nicely iodinated; however, the related *n*-hexane (**1k**) fails to react to appreciable extension. Though yet very preliminary, the previously noted differences for the adsorption of *n*-alkanes on the surface of water might account well for the trend in terms of reactivity in a qualitative sense.[16] This approach offers a convenient method to conduct the iodination of a varied and representative set of hydrocarbons in the presence of water.[17] At the same time, this is a very efficient protocol for directly iodinating alkanes, particularly, considering the high percentage of iodine that is typically incorporated into the structure of the hydrocarbon.

Overall, new reactions and significant experimental advances have been achieved for the iodination of hydrocarbons, which is a notoriously difficult reaction. At the same time, new perspectives for the use of well-established cyclic azidoiodanes have been offered by the present study. The examination of the possible reaction paths followed by using different hypervalent iodine reagents is also of interest with regard to investigating alternative reactive combinations based on simpler reagents. Further studies on the scope and implications of the herein reported chemistry are underway in our laboratories.

Experimental Section

Warning: We have not experienced any explosions while conducting our experiments, either using method A or B (so far, we carried out reactions that lead to about 5 mmol of compounds **2**); however, much care should be taken when working with azides, especially when heating them, as they are potentially explosive compounds.

Method A: All reactions were carried out under a positive pressure of nitrogen. In a typical experiment, I_2 (1.1 mmol, 0.28 g) and $TMSN_3$ (10 %, 13 μL) were sequentially added to a suspension of 1-acetoxy-1,2-benziodoxol-3(1*H*)-one (1 mmol, 0.31 g) in cyclohexane (25 mL). The resulting mixture was stirred at 60 °C (bath temperature) for 15 h. The mixture was allowed to cool and then quenched with aqueous NaOH (5 %, 25 mL). The organic layer was distilled under reduced pressure, and excess cyclohexane was recovered. The distillation residue was diluted with diethyl ether (20 mL) and washed with aqueous $Na_2S_2O_3$ (5 %, 30 mL), brine (30 mL), and dried over anhydrous Na_2SO_4. The solvent was removed at reduced pressure and the resulting oil was further purified by column chromatography, by using a mixture of hexanes as eluent, to afford cyclohexyl iodide **2a** (0.21 g, 0.91 mmol) as an irritating colorless oil.

Method B: In a typical experiment, Ac_2O (1.2 mL), H_2O (0.5 mL), and NaN_3 (0.20 g, 3 mmol) were sequentially added to a cooled solution (water/ice bath) of I_2 (0.25 g, 1 mmol) in toluene (5 mL). H_2O_2 (30 % in water, 0.3 mL) was added and the mixture was vigorously stirred at 40 °C for 13 h. The reaction mixture was poured into a saturated solution of $NaHCO_3$ (20 mL) and washed with aqueous $Na_2S_2O_3$ (5 %, 15 mL). The organic layer was dried over anhydrous Na_2SO_4, and the excess toluene was recovered by distillation. The yellowish residue was purified by column chromatography, by using a mixture of hexanes as eluent, to afford benzyl iodide **2b** (0.41 g, 1.88 mmol) as a lachrymatory pale yellow oil.

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[6] Reaction at 60 °C of **1** (25 mL), 1-acetoxy-1,2-benziodoxol-3(1*H*)-one (1 mmol), I$_2$ (1.1 mmol), and TMSN$_3$ (0.1 mmol, 10 mol % referred to the benziodoxole).

[7] Previously, only one method has been reported incorporating more than one atom of iodine into the alkane for each molecule of the iodine source (CI$_4$), see reference [3b].

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[10] In agreement with this hypothesis, the reaction of **1a** (25 mL), I$_2$ (1 mmol), and **A** (10 mol %, prepared by an independent route), at 60 °C for 24 h, furnished **2a** (99 %, with respect to **A**). No reaction was observed when **1a** and **A** were mixed and heated at 60 °C for 24 h.

[11] For functionalization reactions that incorporate more than 1 mmol of atomic iodine for each mmol of added I$_2$, the possibility of regenerating cyclic iodanyl radicals upon interaction of *o*-iodobenzoic acid with acetyl hypoiodite cannot be ruled out, at present.

[12] For chemistry on hypervalent iodine compounds that has been conducted by using inorganic sources of iodine see, for instance: a) K. C. Nicolaou, T. Montagnon, P. S. Baran, *Angew. Chem.* **2002**, *114*, 1444–1447; *Angew. Chem. Int. Ed.* **2002**, *41*, 1386–1389; NaN$_3$/NaI/CAN convert alkenes into azido iodides: b) V. Nair, T. G. George, V. Sheeba, A. Augustine, L. Balagopal, L. G. Nair, *Synlett* **2000**, 1597–1598; Azido radicals are reasonable intermediates for this transformation. For early work on the oxidation of azide anions to azido radicals by reaction with H$_2$O$_2$/Fe^{II}: c) F. Minisci, R. Galli, *Tetrahedron Lett.* **1962**, 533–538; d) F. Minisci, R. Galli, *Tetrahedron Lett.* **1963**, 357–360.

[13] Arene iodination with I$_2$/CH$_3$CO$_3$H: a) Y. Ogata, K. Aoki, *J. Am. Chem. Soc.* **1968**, *90*, 6187–6191; for the use of H$_2$O$_2$/NaI to functionalize alkenes: b) J. Barluenga, M. Marco-Arias, F. González-Bobes, A. Ballesteros, J. M. González, *Chem. Eur. J.* **2004**, *10*, 1677–1682; for ketone iodinations: c) J. Barluenga, M. Marco-Arias, F. González-Bobes, A. Ballesteros, J. M. González, *Chem. Commun.* **2004**, 2616–2617; sulfonation of methane initiated by H$_2$O$_2$/metal chloride: d) S. Mukhopadhyay, A. T. Bell, *Angew. Chem.* **2003**, *115*, 3098–3101; *Angew. Chem. Int. Ed.* **2003**, *42*, 2990–2993.

[14] Very fast stirring is crucial to this iodination reaction. Lowering the speed of stirring employed to mix the reagents may result in a dramatic decrease of the efficiency of the iodination reaction.

[15] Reaction conditions: hydrocarbon **1** (5 mL), Ac$_2$O (1.2 mL), H$_2$O (0.5 mL), I$_2$ (1 mmol), NaN$_3$ (3 mmol), H$_2$O$_2$ (30 % aqueous solution, 0.3 mL). Reagents were mixed at 0 °C and vigorously stirred. Then the reaction mixture was heated at 40 °C.

[16] a) F. Hauxwell, R. H. Ottewill, *J. Colloid Interface Sci.* **1970**, *34*, 473–479; for conformational equilibria of alkanes in aqueous solution, see: b) H. S. Ashbaugh, S. Garde, G. Hummer, E. W. Kaler, M. E. Paulaitis, *Biophys. J.* **1999**, *77*, 645–654, and references therein.

[17] A single observation on the iodination of cyclohexane upon reaction with degassed aqueous solution of Mn^{III}–tetraphenylporphyrin iodide and PhIO as oxidant, is known to date: C. L. Hill, J. A. Smegal, T. J. Henly, *J. Org. Chem.* **1983**, *48*, 3277–3281.