

# Catalytic Halogen Bond Activation in the Benzylic C–H Bond Iodination with Iodohydantoins

Sascha H. Combe, Abolfazl Hosseini, Lijuan Song, Heike Hausmann, and Peter R. Schreiner\*

Institute of Organic Chemistry, Justus-Liebig University, Heinrich-Buff-Ring 17, 35392 Giessen, Germany

## Supporting Information

**ABSTRACT:** This letter presents the side-chain iodination of electron-deficient benzylic hydrocarbons at rt using *N*-hydroxyph-thalimide (NHPI) as radical initiator and 1,3-diiodo-5,5-dimethyl-hydantoin and 3-iodo-1,5,5-trimethylhydantoin (3-ITMH) as iodine source. Addition of a carboxylic acid increased the reactivity due to complex formation with and activation of 3-ITMH by proton transfer and halogen bond formation. No S<sub>E</sub>Ar reactions were observed under the employed reaction conditions. Our method enables convenient product isolation and gives 50–72% yields of isolated products.

M ethods for the iodination of unactivated alkanes are scarce because the initiation and propagation steps with elemental iodine are endothermic and not counterbalanced by the heat released from iodoalkane formation owing to the relatively C–I low BDEs.<sup>1</sup> Furthermore, the use of I<sub>2</sub> affords hydrogen iodide that may immediately reduce the iodoalkane to the corresponding alkane.<sup>2</sup> Photochemically initiated iodinations suffer from the cleavage of the C(sp<sup>3</sup>)–I bond due to n- to  $\sigma^*$ -excitation at ~250 nm and are therefore unfavorable.<sup>3</sup> This results in iodoalkanes being relatively expensive yet highly valuable reactants in organic synthesis.

Only in 1968 did Tanner and co-workers succeed in synthesizing iodoalkanes from unactivated alkanes by the use of *tert*-butyl hypoiodite.<sup>4</sup> Most existing methods use *tert*-butyl hypoiodite as an intermediate to generate the strongly electrophilic *tert*-butoxy radical or the corresponding iodine-(III) radical (Scheme 1a).<sup>4,5</sup> Unfortunately, *tert*-butyl hypoiodite must be prepared in situ due to its instability.<sup>4</sup> Barluenga et al. used PhI(OAc)<sub>2</sub>, I<sub>2</sub>, and catalytic amounts of trimethylsilyl azide (TMSN<sub>3</sub>) at 60 °C to form PhIOAc radicals that enable homolytic C–H bond cleavage (Scheme 1b).<sup>6</sup> In the next step, I<sub>2</sub> reacts with the carbon radical to form the iodoalkane. Barluenga and co-workers described a second variant consisting of H<sub>2</sub>O<sub>2</sub>, 3 equiv of NaN<sub>3</sub>, and I<sub>2</sub> at 0–40 °C. To date, this is







arguably the best protocol for benzylic substrates bearing an electron-donating group (EDG), but NaN<sub>3</sub> is toxic as well as explosive. Earlier, we described a phase-transfer single electron (SET) approach with crushed NaOH and HCI<sub>3</sub>, generating chain-carrying  $\bullet$ CI<sub>2</sub> radicals.<sup>1a</sup> With this method, aliphatic substrates are easily iodinated in good yields and with very high regioselectivities, which results from the sterically demanding •CI<sub>3</sub> radical. Very recently, Gandelman and Schreiner presented the iodination of aliphatic and benzylic substrates with 1-iodo-3,5,5-trimethylhydantoin (1-ITMH) (1) at 100 °C neat (alkanes) or in benzene in combination with a 3 W LED lamp (Scheme 1c).<sup>7</sup> The benzylic iodoalkanes were thereby transformed in situ to esters as their isolation was low yielding. Commonly, benzyl iodides are synthesized starting from benzyl alcohols<sup>8</sup> or benzyl chlorides<sup>9</sup> because the direct iodination of unactivated alkanes, especially isolation of the pure compound, remains a challenging task (Scheme 1d). Hence, there is still a need for nontoxic, safe, and catalytic methods that enable practical product isolation.

Orazi et al. first used the currently commercially available iodination agent 1,3-diiodo-5,5-dimethylhydantoin (DIH, **2**) in the electrophilic core iodination of arenes.<sup>10</sup> When the authors treated toluene with **2** in combination with benzoyl peroxide (BPO), no benzyl iodide was observed, and they concluded that **2** only serves as a source for electrophilic "I<sup>+</sup>".<sup>10</sup> Indeed, there are only a few examples where **2** can also act as an iodine radical source.<sup>11</sup> The N–I bonds in **1** (BDE = 43.5 kcal mol<sup>-1</sup>),<sup>7</sup> **2** (amide 38.1 kcal mol<sup>-1</sup> and imide 48.7 kcal mol<sup>-1</sup>),<sup>12</sup> and 3-iodo-1,5,5-trimethylhy-dantoin (3-ITMH, **3**) (54.6 kcal mol<sup>-1</sup>)<sup>7</sup> are quite low compared to that of *N*-iodosuccinimide (56.8 kcal mol<sup>-1</sup>)<sup>7</sup> and are therefore ideal candidates for the radical iodination of hydrocarbon C–H

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 Table 1. Initial Evaluation of Reaction Conditions for the

 Side-Chain Iodination of Toluene

	Ph–CH <sub>3</sub> 5	2 (0.375 mm 4 (0.17 e CH <sub>2</sub> Cl <sub>2</sub> ( 25–27	$ \begin{array}{c} \text{pl,1 equiv)} \\ \hline \text{equiv)} \\ \text{2 mL)} \\ \text{°C} \qquad 6 \qquad 4 \end{array} $	N−OH <del>2</del> ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	√N-0⊙ √
entry	<i>t</i> (h)	5 (equiv)	cat. (equiv)	6 (%) <sup>a</sup>	$^{\rm PhCHO}_{(\%)^a}$
1 <sup>b</sup>	16	1.0	$Cu(OAc)_2 \cdot H_2O(0.03)$	11	3
2	16	1.0	$Cu(OAc)_2 \cdot H_2O(0.03)$	19	3
3 <sup>c</sup>	16	1.7	-	18	2
4 <sup><i>d</i></sup>	16	1.7	-	27	3
5 <sup>e</sup>	16	1.7	-	13	<1
6 <sup>f</sup>	16	1.7	-	33	3
$7^g$	16	1.7	-	38	1
8 <sup>h</sup>	16	1.7	-	39	1
9	16	3.4	-	60	3
10	16	6.7	-	69	1
11	2.5	6.7	-	8	-
12	2.5	6.7	PhCO <sub>2</sub> H (0.18)	36	traces
13	2.5	6.7	PhCO <sub>2</sub> H (0.36)	63	2
14	2.5	6.7	100% AcOH (0.36)	62	1
15	2.5	6.7	$Ac_2O(0.18)$	13	1
16	2.5	6.7	diphenic acid (0.36)	65	1
17	2.5	6.7	$p-NO_2C_6H_4CO_2H$ (0.36)	15	<1
18	2.5	6.7	o-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H (0.36)	69	<1
19	2.5	6.7	Cl <sub>2</sub> HCO <sub>2</sub> H (0.36)	47	<1
20	2.5	6.7	CSA (0.36)	12	1
21	2.5	6.7	<i>p</i> -TsOH (0.36)	12	1
22	2.5	6.7	TFA (0.36)	21	<1
23	2.5	6.7	MsOH (0.36)	_	<1
24	2.5	6.7	Ph <sub>3</sub> PS (0.36)	_	-

<sup>*a*</sup>Yield determined by <sup>1</sup>H NMR with dimethyl terephthalate (DMT) as internal standard. <sup>*b*</sup>NIS (0.625 mmol, 1 equiv) used instead of **2**. <sup>*c*</sup>Using 1 mL of CH<sub>2</sub>Cl<sub>2</sub>. <sup>*d*</sup>Using 1.5 mL of CH<sub>2</sub>Cl<sub>2</sub>. <sup>*e*</sup>Using 0.08 equiv of **4**. <sup>*f*</sup>Average <sup>1</sup>H NMR yield of two runs. <sup>*g*</sup>Using 0.25 equiv of **4**. <sup>*h*</sup>Using 0.33 equiv of **4**.

Scheme 2. Substrate Scope for the Side-Chain Iodination of Toluene Derivatives with Yields of Isolated Product Given



bonds. Recently, we presented the side-chain chlorination of aliphatic and benzylic C–H bonds with trichloroisocyanuric acid (TCCA) and *N*-hydroxyphthalimide (NHPI, 4) as radical initiator.<sup>13</sup> This method is not directly transferable to

Table 2. HOMO–SOMO Energy Gap ( $\Delta E$ ) at B3LYP/6-31G(d,p)



Scheme 3. Proposed Reaction Mechanism for the Side-Chain Iodination of Toluene with Computations at the B3LYP-D3/6-31G(d,p) Level of Theory ( $\Delta G_{298K}$  in kcal mol<sup>-1</sup>)



iodinations because triiodoisocyanuric acid (TICA) is not commercially available and its synthesis is cumbersome.<sup>1</sup> Compared to TCCA, TICA is also extremely moisture sensitive.<sup>14b</sup> We have chosen toluene (5) as our model substrate for our new iodination protocol. N-iodosuccinimide (NIS) afforded benzyl iodide (6) in low yield (Table 1, entry 1). However, 2 afforded approximately twice as much product as that of NIS (entry 2). In our TCCA chlorination, a metal catalyst was crucial to perform the reaction. Gratifyingly, no metal catalyst is required with 2, and the yields were higher compared to those with NIS (entry 6). Compound 2 is a strong oxidant that is able to generate phthalimide-N-oxyl (PINO, 7) radical from 4. High dilution provides higher yields (entries 3, 4, and 6). A loading of 4 of  $\sim$ 17 mol % is optimal for a smooth reaction (entry 6); lower loadings down to 8 mol % decrease the yields (entry 5), and higher loadings provide no additional benefit (entries 7 and 8). High substrate loadings also gave higher yields (entries 9 and 10). Using CHCl<sub>3</sub>, 1,2-dichloroethane or CH<sub>3</sub>CN gave inferior results; the latter mainly promoted  $S_{E}Ar$  iodination. To activate the N–I bonds of 2, we screened several carboxylic and sulfonic acids (entries 12-23).<sup>15</sup> In general, carboxylic acids afforded much higher yields than the sulfonic acids, which can be correlated to their  $pK_a$ values. Strong acids such as methanesulfonic acid led to S<sub>E</sub>Ar reactions. These are known to produce "I<sup>+</sup>" and  $I_3^+$ , which give rise to core substitution.<sup>16</sup> With the best reaction conditions in hand (entry 18), we explored the substrate scope of the reaction (Scheme 2). Arenes bearing electron-withdrawing (EWGs) or weakly electron-donating groups (EDGs) gave yields of 35-69%. Yields higher than 69% with 2 could not be achieved, which may be an indication that not all iodine atoms in 2 are active and transferable. To support our assumption, we performed NMR studies with compounds 1-3 (Scheme S1). Compound 1 gave the lowest yield (45%), and 2 and 3 behaved

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Figure 1. NMR studies of the complexation of 3-ITMH (3) and acid in CD<sub>2</sub>Cl<sub>2</sub> (62 mM) at 25 °C.

similarly (71 and 81%, respectively). These results imply that the iodine next to the geminal dimethyl-group in 2 is largely inactive and that the corresponding *N*-centered radical is less reactive for chain propagation.

Therefore, we repeated all of the reactions with method **B** (Scheme 2), substituting **2** with **3**; we also increased the substrate loading, which had the highest influence on the yields as evident from the data analysis (Tables S1 and S2). In general, **3** afforded similar results, giving yields in the range of 50-72%. However, **3** gave higher yields compared to **2** especially for substrates bearing strong deactivating groups.

As electron-rich as well as electron-deficient arenes<sup>17</sup> undergo  $S_EAr$  reactions in the presence of acid, our protocol is quite practical. However, arenes bearing modest to strong electron-donating groups form the corresponding nitroesters. Usually, EWG-substituted arenes undergo  $S_N2$  reactions much faster than EDG-substituted arenes because EWGs lower the  $S_N2$  reaction barrier.<sup>18</sup> Ethylbenzene gave the nitroester in 24% yield; *p*-bromoethylbenzene gave traces of the desired product, whereas *p*-cyanoethylbenzene delivered 59% of corresponding benzyl iodide **15**.

The underlying reactivity is not merely a question of BDEs (ArCH<sub>2</sub>-H: *p*-methyl anisole BDE = 87 kcal mol<sup>-1</sup>; toluene = 88 kcal  $mol^{-1}$ )<sup>19</sup> or radical stability (14 vs 15) but rather a question of frontier orbital interaction (Table 2). The results show that primarily arenes carrying an EWG undergo a smooth reaction (low-lying SOMO). No S<sub>E</sub>Ar products were detected for EWG-containing arenes in preparative mass-balanced reactions; products and starting material (substrate) were recovered with a mass loss of 7-10%. The intermediate electrophilic radicals have to react with a nucleophilic iodine intermediate (Table 2 and Table S6). The three methyl groups of 3 may play an important role because they can donate electron density toward the carbonyl groups. Our computational studies for the side-chain chlorination with TCCA showed that the reaction proceeds preferentially via a carbonyl radical<sup>13</sup> that abstracts a H-radical from the substrate forming an iminol, which tautomerizes to the amide.

On the basis of the results presented here, DFT computations, and literature reports, we propose the mechanism shown in Scheme 3. With the use of 2 or 3, no metal catalyst was needed to start the reaction. Hence, 3 must be able to oxidize 4 to 7. Compound 7 serves in the radical side-chain chlorination only as chain initiator, and higher loadings of 4 did not show significant effects; an additional portion of 4 after 1 h had no beneficial effect, thereby supporting our suggestion. Furthermore, GC-MS analysis revealed the formation of phthalimide. The addition of acid increased the reaction rate considerably (Table 1, entry 18). For whatever reason, p-nitrobenzoic acid did not show the same catalytic efficiency as *o*-nitrobenzoic acid (Table 1, entries 17 and 18). The carboxylic acid does not only serve as a proton source (general acid catalysis) (Figure 1 and Table S3) but is likely to additionally form a halogen bond<sup>20</sup> (for complex 19, also see ToC); both interactions polarize and weaken the N-I bond. ^{16b,21} DFT reveals a bonding angle of  ${\sim}152^{\circ}$ (N-I···O=N), which is slightly below typical bonding angles in association with I  $(160-178^{\circ})^{20b}$  and a short bond distance of 3.06 Å ( $\Sigma$  r(OI<sub>vdw</sub>): 3.50 Å).<sup>22</sup> The dual binding mode is only seen when o-nitrobenzoic acid was used (Figure 1, II vs III). The N-CH<sub>3</sub> group of 3 is shifted downfield more strongly as compared to the geminal dimethyl group (Figure 1, III). This is likely due to the fact that the carbamide group allows for better charge delocalization as compared to that of the amide group. A DFT study (B3LYP/6-311G(d)) of 2 showed that protonation at the carbamide CO is  $\sim 6$  kcal mol<sup>-1</sup> more favorable than at the amide CO.<sup>12</sup> In line with this complexation, the aromatic protons are shifted upfield, gaining electron density from 3 (Figure 1, III vs IV). The <sup>13</sup>C NMR spectrum shows that 3 donates electron density to the carbonyl group of the acid (Figure 1, III vs IV) resulting in a strong upfield shift. Complex formation is also supported by <sup>1</sup>H DOSY NMR (Figure S1 and Table S4). Both molecular components of the mixture are associated with the same diffusion coefficient value (which is lower than the values obtained for the free components in separate experiments). The self-diffusion coefficients for the free molecular components are at least

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half their values in the complex (Table S4). The acid experiences the greatest change in the diffusion coefficient when complexed (a factor of 2), a fact that agrees with its participation in the complex. The measurements were carried out in dilute solution in  $CD_2Cl_2$ , where viscosity variations due to small sample composition changes are negligible. Thus, the significant decrease in diffusion for *o*-nitrobenzoic acid when **3** is present provides strong evidence for the existence of the complex in solution.

Furthermore, I<sub>2</sub> acts as a mild Lewis acid catalyst (halogen bond donor)<sup>23</sup> but is not able to oxidize 4 to 7<sup>24</sup> (Table S5). The monoacid complex (19) is slightly preferred over the diacid complex by 0.3 kcal mol<sup>-1</sup> (Schemes S4 and S5). There is no halogen bond in diacid complex 2a-E (Scheme S5). An acid amount of 2.2 equiv compared to 0.36 equiv gave a rate acceleration of only ~2 even at higher dilution. This result also supports the formation of a monoacid complex. Structure 19 consumes one benzyl radical (20) and forms benzyl iodide (6) as well as a new radical 21 ( $\Delta G_{298K} = 1.3$  kcal mol<sup>-1</sup>), which is able to carry the radical chain (cycle A). The latter reacts further to trimethylhydantoin (22) forming a strong amide bond, which is the driving force of the reaction ( $\Delta G_{298K} =$ -20.0 kcal mol<sup>-1</sup>).

In summary, we present a method for the direct C–H bond iodination of electron-deficient arenes. Iodinating agent 3 can be activated by a carboxylic acid, polarizing the N–I bond through simultaneous hydrogen and halogen bonding. Compared to other methods, our protocol enables convenient product isolation without postmodification.

# ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b03034.

Experimental section, spectra of all compounds, computations and procedures, Cartesian coordinates, and absolute energies of all optimized structures (PDF)

#### AUTHOR INFORMATION

#### **Corresponding Author**

\*E-mail: prs@uni-giessen.de

**ORCID** 

Peter R. Schreiner: 0000-0002-3608-5515 Notes

The authors declare no competing financial interest.

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