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$NaIO_4$–KI–NaN_3 as a new reagent system for C–H functionalization in hydrocarbons

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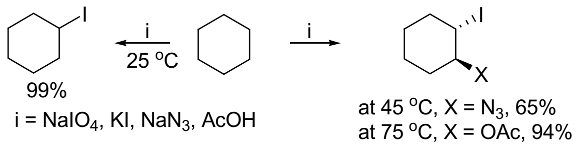
ABSTRACT

The $NaIO_4$–KI–NaN_3 combination has been found to be an efficient, reliable, and inexpensive reagent system for mono- and 1,2-difunctionalization of hydrocarbons via C–H bond activation to afford vicinal azido- and acetoxy iodinations of cyclic hydrocarbons.

Direct and selective replacement of C–H bonds in hydrocarbons with C–C, C–O, C–N, and C–X groups is an important and long-standing goal in chemistry.[1] Generally, for monofunctionalization of unactivated C–H bonds, catalytic systems such as organometallic compounds,[2a] metallo-porphyrin complexes,[2b] superacids,[2c] Gif and Gif-Orsay systems,[2d] $MeReO_3/H_2O_2$,[2e] OsO_4,[2f] polyoxometallates,[2g] and other systems[1] have been reported. In particular, a new, effective method for 1,2-functionalization of unactivated C–H bonds in a single step, which represents a major challenge for chemists, has been developed by Barluenga's group.[3] In addition, free-radical iodinations of hydrocarbons with iodine, despite its endothermic nature, have emerged as a useful route for the activation of C–H bonds in hydrocarbons.[4]

During the course of our study on $NaIO_4$-mediated oxidative halogenations,[5] we noticed that regiospecific addition of I–N_3,[6] generated in situ, onto styrenes took place in an *anti*-Markovnikov fashion, suggesting a probable radical pathway.[7] This prompted us to explore the effectiveness of the $NaIO_4$–KI–NaN_3 combination in the C–H activation of alkanes. We report here the use of $NaIO_4$–KI–NaN_3 to selectively functionalize the C–H bonds of hydrocarbons to produce iodoalkanes **2a–g**, 1-acetoxy- or 1-azido-2-iodocycloalkanes **3a–d** (Scheme 1) or benzyl azides **5**, in excellent yields upon reaction with the respective hydrocarbons.

When cyclohexane was treated with $NaIO_4$, KI, and NaN_3 (all 1 equiv) in acetic acid at 25 °C, iodocyclohexane (**2a**) was isolated in 32% yield; however, the yield was increased to 99% when 3 equiv of NaN_3 was used. This novel iodination[8] is successful for a variety of alkanes including cyclic and acyclic, and its completion is readily ascertained by a distinct color change in the reaction from dark brown to colorless. The presence of both $NaIO_4$ and NaN_3 was essential for obtaining high yields of iodoalkanes **2a–g**. Interestingly, for linear alkanes, an improved selectivity was observed as only the methylene positions were iodinated (Table 1, entries **e–g**).



Scheme 1. $NaIO_4$-mediated C–H activation of cyclohexane.

Surprisingly, for cyclooctane under the same reaction conditions, the reaction took a different course to furnish **3a** in 60% yield along with **2d** in 15% yield (Table 2).

However, with 6 molar equiv of NaN_3, **3a** was obtained in 85% yield with *syn:anti* ratio of 2:1. In contrast, vigorous stirring of 2 equiv each of $NaIO_4$ and NaN_3 along with KI (1 equiv) gave only **2d** in 99% yield (Table 1). It was also found that both $NaIO_4$ and NaN_3, in appropriate concentrations, were critical in determining product selectivities. Thus, for cyclohexane, at 45 °C, with 3 molar equiv of NaN_3, **2a** (81%) was obtained along with **3b** (10%) and **3c** (5%), while use of 6 molar equiv of NaN_3 resulted in improved product selectivity: **3b** (62%) and **3c** (35%). At 75 °C, an excellent yield of **3c** (94%) was realized with $NaIO_4$ (2 equiv; 10 mmol). For cyclopentane, at 45 °C, only cyclopentyl monoacetate (**5f**) was

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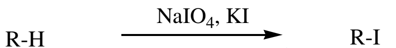
Table 1

$NaIO_4$-mediated iodination of alkanes with KI and NaN_3[a]



$$\underset{\mathbf{1}}{\text{R-H}} \xrightarrow[\text{NaN}_3\text{, AcOH, 25 °C}]{\text{NaIO}_4\text{, KI}} \underset{\mathbf{2a\text{-}g}}{\text{R-I}}$$

Entry	R–H (**1**)	*t* (h)	Yield of **2**[b] (%)
a	Cyclohexane	8	99
b	Cyclopentane	6	98
c	Cycloheptane	8	99
d	Cyclooctane	4	99[c]
e	*n*-Pentane	9	99 (2:1)[d]
f	*n*-Hexane	6	98 (1.1:1)[e]
g	*n*-Heptane	8	97 (2.5:2.2:1)[f]

[a] Reaction conditions: alkane (5 mL), $NaIO_4$ (5 mmol), KI (5 mmol), NaN_3 (15 mmol), glacial AcOH (15 mL), 25 °C.

[b] Yield was calculated based on KI.

[c] 2 equiv each of $NaIO_4$ and NaN_3 used.

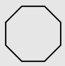
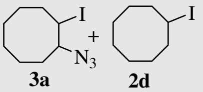
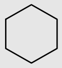
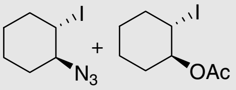
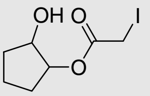
[d] 2-I:3-I pentane.

[e] 2-I:3-I hexane.

[f] 2-I:3-I:4-I heptane; (ratios determined by ^{1}H NMR and GC).

Table 2

$NaIO_4$-mediated 1,2-difunctionalization of cycloalkanes with KI and NaN_3[a]

Entry	R–H (**1**)	NaN_3 (equiv)	*t* (h)	*T* (°C)	Yield of **3**[b] (%)	
1					 **3a** **2d**	
		3	4	25	60	15
		6	4	25	85[c]	–
2					 **3b** **3c**	
		3	24	45	10	5[d]
		6	24	45	62	35
		3	10	75	–	70[e]
		3	10	75	–	94[f]
3					 **3d**	
		3	10	45	–[g]	
		6	30	45	50[h,i]	

[a] Reaction conditions: cycloalkane (5 mL), $NaIO_4$ (5 mmol), KI (5 mmol), glacial AcOH (15 mL).

[b] Yield was calculated based on KI.

[c] *syn:anti* = 2:1 by ^{1}H NMR.

[d] **2a** was formed in 81% yield.

[e] **2a** was also formed in 25% yield.

[f] 2 equiv of $NaIO_4$ was used.

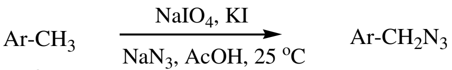
[g] cyclopentyl acetate **5f** was formed in 95% yield.

[h] Cyclopentyl acetate **5f** was also formed in 46% yield.

[i] Stereochemistry was not assigned.

Table 3

NaIO4-mediated azidation at the benzylic C–H bond of alkyl arenes[a]



$$\underset{\mathbf{4}}{\text{Ar-CH}_3} \xrightarrow[\text{NaN}_3\text{, AcOH, 25 °C}]{\text{NaIO}_4\text{, KI}} \underset{\mathbf{5a\text{-}e}}{\text{Ar-CH}_2\text{N}_3}$$

Entry	Arene (**4**)	*t* (h)	Benzyl azide (**5**)	Yield[b] (%)
a	Toluene	8	Benzyl azide	95
b	*o*-Xylene	8	2-Methylbenzyl azide	85
c	*m*-Xylene	7	3-Methylbenzyl azide	90
d	*p*-Xylene	8	4-Methylbenzyl azide	93
e	Mesitylene	7	3,5-Dimethylbenzyl azide	89

[a] Reaction conditions: arene (5 mL), $NaIO_4$ (5 mmol), KI (5 mmol), NaN_3 (30 mmol), glacial AcOH (20 mL), 25 °C.

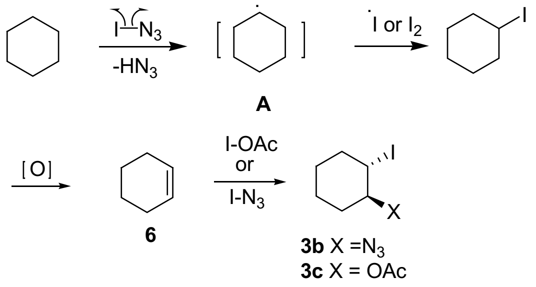
[b] Yield was calculated based on KI.

obtained in 95% yield, whereas an increase of azide concentration (6 molar equiv) gave an unusual 1, 2-dihydroxyiodo derivative[9] **3d** in 50% yield along with **5f** (46%) (Table 2). In the case of cycloheptane, an increase of either the temperature or the azide concentration resulted in only cycloheptyl monoacetate in 96% yield. Overall, increasing the temperature facilitates oxidative elimination of the iodoalkane to furnish an alkene, thereby giving higher yields of difunctionalized products. However, in the case of cycloheptane and cyclopentane, nucleophilic substitution becomes a favorable process.[10]

Direct azidation via functionalization at Ar–C–H bonds is an atom economical route in organic synthesis.[11] A recent report on direct azidation of activated arenes using polymer-supported iodine azide has established that a certain electron-donating capacity is needed at the benzylic position for the reaction to occur.[12] With the $NaIO_4$–KI–NaN_3 system (1:1:3 molar ratio), we found that toluene was functionalized smoothly at the benzylic position to give benzyl azide (85%) along with benzyl acetate (10%). Further, on increasing the concentration of azide (6 equiv), exclusive formation of monobenzyl azide **5a** (95%) was realized.[13] Notably, no polyazidation took place for other alkylarenes even if greater equivalents of NaN_3 were used (Table 3).

Mechanistically, $NaIO_4$ oxidizes KI as well as NaN_3 simultaneously, to liberate I_2[5] and an azide radical,[14] respectively, combination of which results in the formation of I–N_3. To confirm the formation of I_2, the alkane was treated with molecular iodine instead of KI and we found that similar results were indeed obtained. Homolysis of I–N_3[12c] provides an azide radical, which abstracts a proton from alkanes to produce alkyl radical **A**. Combination of radical **A** with I_2 followed by oxidative elimination of the resulting alkyl iodide[15] generates alkene **6** (confirmed by GC analysis). Addition of either I–N_3 or I–OAc across the double bond of **6** produces **3b** and **3c**, respectively (Scheme 2). Evidence for the radical pathway is deduced from the following experiments: (i) no reaction took place in the presence of *N-tert*-butyl-α-phenylnitrone, a radical scavenger;[12c] (ii) regioselective azidoiodination of styrene under the reaction conditions led to the isolation of 2-azido-1-iodo-ethylbenzene.[6] In the case of direct azidation of alkyl arenes, the involvement of a benzyl radical followed by a benzyl cation[12a] is similarly proposed.

In conclusion, we have described $NaIO_4$–KI–NaN_3 as a new efficient system suitable for mono and 1,2-difunctionalization of hydrocarbons via C–H bond activation. In particular, vicinal azido-



Scheme 2. Proposed mechanism.

and acetoxy iodinations of cyclic hydrocarbons in high yield and selectivity are unique and unprecedented. A high yield direct azidation at the benzylic position in less activated alkyl arenes has been demonstrated under ambient conditions.

Acknowledgments

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8. *General experimental procedure for iodination of alkanes*: To a suspension of NaN_3 (0.975 g, 15 mmol) and KI (0.830 g, 5 mmol) in glacial acetic acid (20 ml) at 25 °C was added $NaIO_4$ (1.069 g, 5 mmol), and the reaction mixture was stirred for 5 min during which time the reaction turned dark brown in color. Alkane (5 ml) was then added, and the reaction mixture was stirred at the same temperature for 8 h until the mixture became colorless. The reaction mixture was poured into water (100 ml) and extracted with CH_2Cl_2 (3×50 ml)). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (50 ml) and aqueous $Na_2S_2O_3$ (5%, 50 ml), dried over an hyd. Na_2SO_4, and concentrated. Unreacted alkanes were recovered by simple distillation under reduced pressure to give the crude product, which was purified by column chromatography (silica gel 60-120 mesh) using petroleum ether as eluent to afford the pure product **2a**–**g**.
   Spectral data for compound **2a**: Colorless oil; Yield: 99%; IR ($CHCl_3$) ν 2933, 2854, 1448, 1215, 1172, 1095, 987, 759, 669, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.37–1.49 (m, 3H), 1.64–1.74 (m, 3H), 1.93–2.05 (m, 2H), 2.13–2.20 (m, 2H), 4.30–4.43 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.14, 27.22, 32.66, 39.51; Anal. calcd. for $C_6H_{11}I$: C, 34.31; H, 5.28. Found C, 34.30; H, 5.30.
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13. *General experimental procedure for azidation of alkyl arenes*: To a suspension of NaN_3 (1.950 g, 30 mmol) and KI (0.830 g, 5 mmol) in glacial acetic acid (20 ml) at 25 °C was added $NaIO_4$ (1.069 g, 5 mmol), and the reaction mixture was stirred for 5 min during which time the reaction turned dark brown in color. Alkyl arene (5 ml) was added and the reaction mixture was stirred at the same temperature for 8 h. The reaction mixture was poured into water (100 ml) and extracted with CH_2Cl_2 (3×50 ml)). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (50 ml) and aqueous $Na_2S_2O_3$ (5%, 50 ml), dried over anhyd. Na_2SO_4, and concentrated. Unreacted alkyl arene was recovered by simple distillation under reduced pressure to give the crude product, which was purified by column chromatography (silica gel 60–120 mesh) using petroleum ether as eluent to afford the pure product **5a**–**e**.
   Spectral data for compound **5a***:* Colorless liquid; Yield: 95%; IR ($CHCl_3$) ν 3032, 3015, 2930, 2877, 2097, 1605, 1586, 1496, 1455, 1255, 1217, 758, 699, 668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.33 (s, 2H), 7.34–7.43 (m 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 54.70, 128.15, 128.23, 128.76, 135.30; Anal. calcd. for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found C, 63.00; H, 5.40; N, 31.20.
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