Regiospecific Azidoiodination of Alkenes with Sodium Periodate, Potassium Iodide, and Sodium Azide: A High-Yield Synthesis of β-Iodoazides

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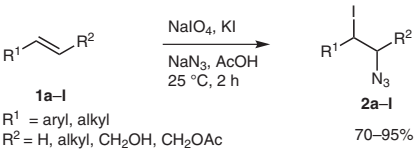
Received 19 July 2010; revised 17 August 2010

Abstract: The combination of sodium periodate, potassium iodide, and sodium azide has been found to be an efficient, simple, and inexpensive reagent system for azidoiodination of alkenes. The regiospecific 1,2-azidoiodination proceeds in an anti-Markovnikov fashion to produce β-iodoazides in excellent yields.

Key words: azides, alkenes, azidoiodination, β-iodoazides, regiospecific



Scheme 1 Sodium periodate mediated azidoiodination of alkenes

The 1,2-functionalizations of olefins by the selective addition of azide and iodo groups (azidoiodination) that proceeds in a highly regio- and stereoselective manner are of current interest in organic synthesis. The resulting β-iodoazides can readily be transformed into versatile intermediates such as vinyl azides,[1] amines,[2] aziridines,[3] tetrazoles,[4] etc., which display antituberculosis,[5a] antibiotic,[5b] anticancer,[5c] immunostimulating,[5d] and anti-HIV[5e] activities. The general methods of synthesis for β-iodoazides consist among others, reaction of alkenes with IN_3, which was prepared in situ by the reaction of either I_2 with AgN_3 or NaN_3 and ICl in polar solvents.[6] However, a considerable drawback associated with IN_3 as a reagent, is its potentially explosive nature, which inhibits its widespread use. Although other reagent systems like I_2/NaN_3,[7] $IPy_2BF_4/TMSN_3$,[8] $PhI(OAc)_2/TMSN_3/Et_4NI$,[9a] and polymer-bound IN_3[9b] can serve as azidoiodination reagents, they all preferentially produce Markovnikov products. Only a couple of protocols like NaN_3/NaI/CAN[10] and NaN_3/KI/oxone/wet Al_2O_3[11] proceed to give anti-Markovnikov addition products when carried out with olefins. However, these methods too suffer from certain drawbacks such as use of expensive reagents and large excess of oxidants and halide sources. Hence, a practical method that involves less toxic yet readily available reagents is of paramount importance. This paper describes one such process, in which an excellent regiospecific azidoiodination of alkenes takes place using sodium periodate as the stoichiometric oxidizing agent and sodium azide and potassium iodide as the azide and iodine sources, respectively, in acetic acid as solvent (Scheme 1).

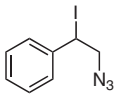
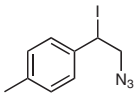
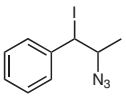
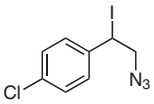
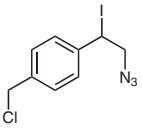
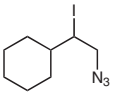
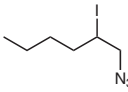
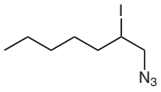
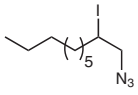
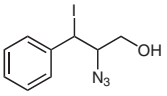
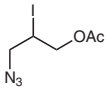
In continuation of our studies on sodium periodate mediated oxidative halogenation of aromatics,[12] halohydroxylation of alkenes,[13] and C–H activation of hydrocarbons,[14] we reasoned that the sodium periodate, potassium iodide, and sodium azide combination can be an effective, simple reagent system for the regiospecific 1,2-azidoiodination of styrene. Thus, when styrene was treated initially with sodium periodate, potassium iodide, and sodium azide (all equimolar) in acetic acid at 25 °C, the corresponding 1-(2-azido-1-iodoethyl)benzene was isolated in 33% yield. However, this yield was increased to 95% when the stoichiometry of sodium azide was increased to three equivalents (Scheme 1).[15] This prompted us to explore the effectiveness of the sodium periodate, potassium iodide, and sodium azide system in the 1,2-azidoiodination of several alkenes. This new azidoiodination procedure was indeed found to be quite general for a variety of olefins and the results of this study are summarized in Table 1.

As can be seen from Table 1, a variety of alkenes **1a–l** (aliphatic, styrenic, allylic, and disubstituted) underwent azidoiodinations to give the corresponding β-iodoazides **2a–l** in excellent yields. It is interesting to note that the regiochemistry of the addition, for all the cases examined, proceeded in an anti-Markovnikov fashion, indicating a possible radical pathway.[16] Internal olefins such as β-methylstyrene, cyclohexene, and cinnamyl alcohol gave products in excellent yields with diastereoselectivities reaching up to 1:4 (Table 1, entries **c**, **f**, and **k**) as confirmed by their ^1H NMR spectra. Terminal functionalized olefin such as allyl acetate also underwent regiospecific azidoiodination in 92% yield. However, no reactions took place in the case of conjugated alkenes with electron-withdrawing groups, which may be a limitation of this method. Mechanistically, $NaIO_4$ oxidizes both KI and NaN_3 simultaneously to liberate I_2[12] and an azide radical,[17] respectively; combination of which probably results in the formation of IN_3 (Scheme 2).[18]

Homolysis of IN_3[19] provides an azide radical, which then adds onto alkenes to produce a more stable alkyl radical species **A**, thus controlling the regiochemistry of the process. The combination of alkyl radical with either I_2 or iodine radical results in the formation of β-iodoazides **2a–l**.

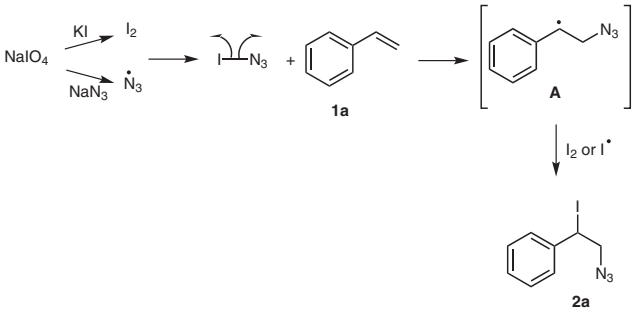
SYNTHESIS 2010, No. 22, pp 3879–3882
Advanced online publication: 14.09.2010
DOI: 10.1055/s-0030-1258250; Art ID: Z18410SS

Table 1 $NaIO_4$-Mediated Regiospecific Azidoiodination of Alkenes[a]

Entry	Alkenes **1**	Products **2**	Yield (%)[b]
a	styrene		95
b	4-methylstyrene		70
c	β-methylstyrene		95[c]
d	4-chlorostyrene		92
e	4-chloromethylstyrene		85
f	cyclohexene		93[d]
g	vinylcyclohexane		88
h	hex-1-ene		93
i	hept-1-ene		94
j	dec-1-ene		90
k	*trans*-cinnamyl alcohol		90[c]
l	allyl acetate		92

[a] Reaction conditions: alkene (5 mmol), KI (5 mmol), $NaIO_4$ (5 mmol), NaN_3 (15 mmol), glacial AcOH (15 mL), 25 °C, 2 h.
[b] Isolated yield.
[c] Ratio *syn*/*anti* = 1:1.
[d] Ratio *syn*/*anti* = 1:4.

In conclusion, we have developed a simple procedure with $NaIO_4$/KI/NaN_3 as a new combination for the 1,2-azidoiodination of alkenes that provides a mild, efficient entry to vicinal azidoiodoalkanes in high yields under ambient conditions. The azidoiodination reaction proceeds to give β-iodoazides **2a–l** in a regiospecific manner.



Scheme 2 Proposed mechanistic pathway for the azidoiodination

All reactions were carried out under an inert atmosphere. All the chemicals (AR grade) were obtained from commercial sources and used without further purification. Petroleum ether (PE) refers to the fraction with bp 60–80 °C. Reaction progress was monitored by TLC using aluminum plates precoated with silica gel 60 F_{254} (0.25 mm, Merck). Column chromatography was performed on silica gel (60–120 mesh) using PE–EtOAc mixtures as the eluent. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker AC 200, AV 400 and DRX 500 spectrometers (^1H at 200 or 500 MHz; ^{13}C at 50, 100 or 125 MHz) with $SiMe_4$ as internal standard.

Azidoiodination of Alkenes; General Procedure

To a suspension of NaN_3 (0.975 g, 15 mmol) and KI (0.830 g, 5 mmol) in AcOH (20 mL) at 25 °C was added $NaIO_4$ (1.069 g, 5 mmol) and the reaction mixture was stirred for 5 min when a dark brown color was observed. This was followed by the addition of alkene **1a–l** (5 mmol) and the entire reaction mixture was stirred at the same temperature for 2 h. After the reaction was complete as monitored by TLC, the mixture was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (50 mL), aq 5% $Na_2S_2O_3$ (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography (packed with silica gel 60–120 mesh) using petroleum ether as eluent to afford the pure product **2a–l** (Table 1).

1-(2-Azido-1-iodoethyl)benzene (2a)

Yield: 95%; pale yellow oil.

IR ($CHCl_3$): 693, 1257, 1446, 1605, 2100, 2921, 3027 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.94 (d, *J* = 7.7 Hz, 2 H), 5.14 (t, *J* = 7.7 Hz, 1 H), 7.30–7.45 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.8, 58.5, 127.4, 128.7, 128.9, 140.1.

Anal. Calcd for $C_8H_8IN_3$: C, 35.19; H, 2.95; N, 15.39. Found: C, 35.10; H, 2.90; N, 15.44.

1-(2-Azido-1-iodoethyl)-4-methylbenzene (2b)

Yield: 70%; pale yellow oil.

IR ($CHCl_3$): 1257, 1446, 2101, 2920, 3027 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 3.87 (d, *J* = 7.7 Hz, 2 H), 5.09 (t, *J* = 7.7 Hz, 1 H), 7.10 (d, *J* = 7.8 Hz, 2 H), 7.27 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2, 28.1, 58.6, 127.3, 129.5, 137.2, 138.5.

Anal. Calcd for $C_9H_{10}IN_3$: C, 37.65; H, 3.51; N, 14.64. Found: C, 37.70; H, 3.48; N, 14.60.

1-(2-Azido-1-iodopropyl)benzene (2c)
Yield: 95%; pale yellow oil; mixture of *anti*/*syn* (1:1).

IR ($CHCl_3$): 1258, 1605, 1458, 2101, 2990 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.4 Hz, 3 H), 1.52 (d, *J* = 6.4 Hz, 3 H), 3.74–3.99 (m, 2 H), 4.91 (d, *J* = 7.0 Hz, 1 H), 4.96 (d, *J* = 8.0 Hz, 1 H), 7.26–7.40 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2, 28.1, 58.6, 127.3, 129.5, 137.2, 138.5.

Anal. Calcd for $C_9H_{10}IN_3$: C, 37.65; H, 3.51; N, 14.64. Found: C, 37.70; H, 3.48; N, 14.62.

1-(2-Azido-1-iodoethyl)-4-chlorobenzene (2d)
Yield: 92%; pale yellow oil.

IR ($CHCl_3$): 693, 1257, 1489, 1589, 2100 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.88–3.94 (m, 2 H), 5.10 (dd, *J* = 8.2, 7.0 Hz, 1 H), 7.30–7.40 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.0, 58.5, 128.8, 129.1, 134.4, 138.7.

Anal. Calcd for $C_8H_7ClIN_3$: C, 31.25; H, 2.29; N, 13.66. Found: C, 31.30; H, 2.25; N, 13.68.

1-(2-Azido-1-iodoethyl)-4-chloromethylbenzene (2e)
Yield: 85%; pale yellow oil.

IR ($CHCl_3$): 1257, 1489, 2101, 2920, 3027 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.92 (d, *J* = 6.9 Hz, 2 H), 4.55 (s, 2 H), 5.12 (t, *J* = 7.2 Hz, 1 H), 7.32–7.43 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.8, 45.3, 58.5, 127.9, 129.0, 137.9, 140.4.

Anal. Calcd for $C_9H_9ClIN_3$: C, 33.62; H, 2.82; N, 13.07. Found: C, 33.55; H, 2.85; N, 13.01.

1-Azido-2-iodocyclohexane (2f)
Yield; 93%; pale yellow oil; mixture of *anti*/*syn* (4:1).

IR ($CHCl_3$): 669, 769, 923, 1217, 1257, 1448, 2100, 2860, 2939 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.31–1.57 (m, 4 H), 1.99–2.50 (m, 4 H), 3.46–3.58 (m, 1 H), 3.90–4.03 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.7, 26.9, 31.8, 33.2, 38.3, 67.1.

Anal. Calcd for $C_6H_{10}IN_3$: C, 28.70; H, 4.01; N, 16.74. Found: C, 28.64; H, 4.10; N, 16.78.

1-(2-Azido-1-iodoethyl)cyclohexane (2g)
Yield 88%; pale yellow oil.

IR ($CHCl_3$): 669, 769, 923, 1217, 1257, 1448, 2102, 2860, 2939 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.02–1.45 (m, 6 H), 1.63–1.93 (m, 5 H), 3.63–3.82 (m, 2 H), 4.07–4.15 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.6, 25.8, 26.0, 30.5, 32.8, 41.0, 42.1, 56.5.

Anal. Calcd for $C_6H_{14}IN_3$: C, 34.42; H, 5.06; N, 15.05. Found: C, 34.50; H, 5.01; N, 14.98.

1-Azido-2-iodohexane (2h)
Yield 93%; pale yellow oil.

IR ($CHCl_3$): 667, 769, 925, 1258, 1446, 2103, 2939 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.9 (t, *J* = 6.9 Hz, 3 H), 1.27–1.52 (m, 4 H), 1.73–1.84 (m, 2 H), 3.60–3.83 (m, 2 H), 4.04–4.17 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8, 22.3, 28.4, 31.5, 37.1, 58.9.

Anal. Calcd for $C_6H_{12}IN_3$: C, 28.47; H, 4.78; N, 16.60. Found: C, 28.50; H, 4.69; N, 16.65.

1-Azido-2-iodoheptane (2i)
Yield 94%; pale yellow oil.

IR ($CHCl_3$): 669, 769, 923, 1257, 1448, 2102, 2939 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.9 (t, *J* = 6.6 Hz, 3 H), 1.27–1.50 (m, 6 H), 1.69–1.84 (m, 2 H), 3.57–3.80 (m, 2 H), 4.04–4.17 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 22.3, 28.8, 30.7, 32.2, 37.0, 58.9.

Anal. Calcd for: $C_7H_{14}IN_3$: C, 31.48; H, 5.28; N, 15.73. Found: C, 31.40; H, 5.33; N, 15.65.

1-Azido-2-iododecane (2j)
Yield: 90%; pale yellow oil.

IR ($CHCl_3$): 668, 770, 923, 1257, 1448, 2103, 2939 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.9 (t, *J* = 6.1 Hz, 3 H), 1.28–1.51 (m, 12 H), 1.72–1.82 (m, 2 H), 3.59–3.80 (m, 2 H), 4.01–4.11 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.8, 28.7, 29.2, 29.3, 31.8, 32.0, 37.1, 59.0.

Anal. Calcd for $C_{10}H_{20}IN_3$: C, 38.85; H, 6.52; N, 13.59. Found: C, 38.75; H, 6.60; N, 13.65.

2-Azido-3-iodo-3-phenylpropan-1-ol (2k)
Yield: 90%; pale yellow oil; mixture of *anti*/*syn* (1:1).

IR ($CHCl_3$): 757, 1153, 1217, 1258, 1458, 2096, 2927, 3004, 3330 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.36 (br s, 2 H), 3.40–3.49 (m, 1 H), 3.59–3.66 (m, 1 H), 3.75–3.94 (m, 2 H), 4.02–4.17 (m, 2 H), 5.13 (d, *J* = 8.5 Hz, 1 H), 5.16 (d, *J* = 9.2 Hz, 1 H), 7.28–7.48 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.9, 32.1, 63.1, 64.8, 68.6, 70.0, 127.8, 128.2, 128.6, 128.9, 129.0, 140.1, 140.2.

Anal. Calcd for $C_9H_{10}IN_3O$: C, 35.66; H, 3.33; N, 13.86. Found: C, 35.70; H, 3.30; N, 13.85.

3-Azido-2-iodopropyl Acetate (2l)
Yield: 92%; pale yellow oil.

IR ($CHCl_3$): 669, 769, 923, 1257, 1448, 1735, 2101, 2940 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.10 (s, 3 H), 3.74–3.82 (m, 2 H), 4.15–4.37 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.5, 23.8, 55.3, 65.9, 169.3.

Anal. Calcd for $C_5H_8IN_3O_2$: C, 22.32; H, 3.00; N, 15.62. Found: C, 22.38; H, 2.98; N, 15.73.

Acknowledgment

The author P.V.C. thanks CSIR for the award of a fellowship and DST, New Delhi (sanction no.SR/S1/OC-72/2006) for financial support. The authors also thank Dr. B. D. Kulkarni, Head, CE-PD for his constant encouragement and support.

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