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$NaIO_4$–NaN_3-mediated diazidation of styrenes, alkenes, benzylic alcohols, and aryl ketones

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ABSTRACT

Sodium periodate and sodium azide combination has been found to be an excellent reagent system suitable for the direct diazidation of styrenes, alkenes, benzylic alcohols, and aryl ketones to produce the corresponding vicinal and geminal diazides respectively in high yields under mild reaction conditions.

Vicinal diazides are important precursors to 1,2-diamines,[1] which are useful functional groups present in a variety of natural products, pharmaceutical substances (e.g., D-(+)-biotin),[2] etc. In addition, 1,2-diamines find increasing utilization in organic synthesis either as chiral auxiliaries or as metallic ligands especially in the field of catalytic asymmetric synthesis.[3] Quite recently, a few useful methods of introducing vicinal diazide functionality onto alkenes have been reported.[4] These include combinations like Mn^{3+}–NaN_3 (large excess)-AcOH[5] or TFA,[6] Fe^{2+}–H_2O_2–NaN_3,[7] PhIO–NaN_3–AcOH,[8] and S_N2 displacements involving multi-step reactions.[9] However, some of them suffer from drawbacks like use of expensive metal salts and oxidants, low yields, and multistep reaction sequences. In this Letter, we wish to report a new $NaIO_4$-mediated procedure for the direct diazidation of alkenes and aryl ketones with NaN_3 that affords vicinal and geminal diazides (**2** and **4**) respectively in excellent yields (Tables 1 and 2).

In continuation of our studies on $NaIO_4$-mediated oxidative functionalization of organic compounds (e.g., halogenation of aromatics,[10a] halohydroxylation of alkenes,[10b] C–H activation of hydrocarbons,[10c] and quite recently, azidoiodination of alkenes[10d]), we reasoned that, in the absence of KI, sodium periodate/sodium azide/DMSO–AcOH combination can be an effective and simple reagent system for the 1,2-diazidation of alkenes. Accordingly, when styrene (**1a**) was heated initially with $NaIO_4$ and NaN_3 (1 equiv each) in DMSO–AcOH at 75 °C, the corresponding 1,2-diazido-1-phenylethane (**2a**) was isolated in 35% yield. However, this yield was increased to 85% when the stoichiometry of NaN_3 was increased to 3 equiv (Scheme 1). After several experimentation with alkenes, the best yields of diazides could be obtained with the optimum combination of NaN_3 (3 equiv) and $NaIO_4$ (1 equiv). This prompted us to further examine the effectiveness of the $NaIO_4$–NaN_3 in DMSO–AcOH system in the 1,2-diazidation of several alkenes. This new diazidation procedure was indeed found to be quite general for a variety of alkenes and the results of the study are presented in Table 1.

Several styrenic substrates as well as aliphatic olefins including linear and cyclic alkenes gave good yields of the corresponding vicinal 1,2-diazides (entries a–o). In the case of internal olefins, the diazides were also obtained in high yields with dr = 1:1 as determined from their ^1H NMR spectra. However, no reaction took place in the case of α,β-unsaturated carbonyl compounds (e.g., cinnamic esters and (*R*)-(−)-carvone) as well as sterically hindered alkenes (e.g., α-pinene), which may be a limitation of this method.

We further extended the scope of this reagent system to several aryl ketones **3** and some of the corresponding benzylic alcohols for the direct azidation. As can be seen from Table 2, linear and cyclic aryl ketones with α-methylene group (–CO–CH_2–) underwent selective oxidative diazidation with $NaIO_4$ (1 equiv) and NaN_3 (3 equiv) in AcOH–DMSO (1:4) as solvent at 75 °C, to give α,α-diazido aryl ketones (**4a–f**) in 91–96% yields (Table 2). Isobutyrophenone (entry f) produced the corresponding α-monoazido ketone **4f** in 35% yield. At low temperatures, no reaction took place and only starting material was recovered. However, at higher temperatures the formation of monoazidoketone was not detected (as

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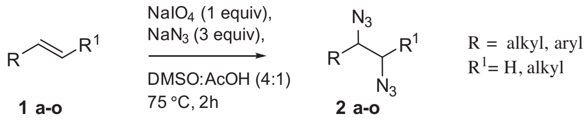
Table 1
NaIO$_4$-mediated 1,2-diazidation of styrenes and alkenes with NaN$_3$[a]

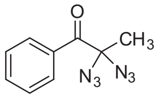
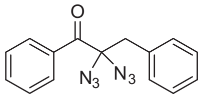
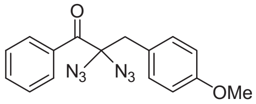
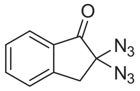
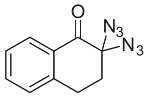
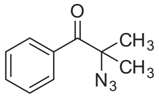


R = alkyl, aryl
R^1= H, alkyl

Entry	Olefins (**1a**–**o**)	Vicinal diazides (**2a**–**o**)	Yield[b] (%)
a	Styrene	1,2-Diazido-1-phenylethane	85
b	3-Methoxystyrene	1,2-Diazido-1-(3-methoxyphenyl)ethane	90
c	4-Methylstyrene	1,2-Diazido-1-(4-methylphenyl)ethane	87
d	3,4-Methylenedioxy-styrene	5-(1,2-Diazidoethyl)benzo[1,3]dioxole[16]	90
e	2-Chlorostyrene	1,2-Diazido-1-(2-chlorophenyl)ethane	85
f	4-Bromostyrene	1,2-Diazido-1-(4-bromophenyl)ethane	90
g	4-Fluorostyrene	1,2-Diazido-1-(4-fluorophenyl)ethane[17]	89
h	1-Cyclohexylethylene	1,2-Diazido-1-cyclohexylethane	80
i	Hex-1-ene	1,2-Diazidohexane	70
j	Hept-1-ene	1,2-Diazidoheptane	68
k	Dec-1-ene	1,2-Diazidodecane	63
l	1-Indene	1,2-Diazidoindane	75[c]
m	*trans*-Cinnamyl alcohol	2,3-Diazido-3-phenylpropan-1-ol	78[c]
n	Cyclohexene	1,2-Diazidocyclohexane	49[c,d]
o	Cyclooctene	1,2-Diazidocyclooctane	60[c]

Reaction conditions:
[a] alkene (5 mmol), NaIO$_4$ (5 mmol), NaN$_3$ (15 mmol), 20 ml of DMSO–AcOH (4:1), 75 °C, 2 h.
[b] Yield refers to isolated yield after column chromatography.
[c] Refers to 1:1 ratio of *syn:anti* isomers of 1,2-diazide.
[d] Excess of cyclohexene was used.

Table 2
NaIO$_4$-mediated α,α-diazidation of aryl ketones with NaN$_3$[a]

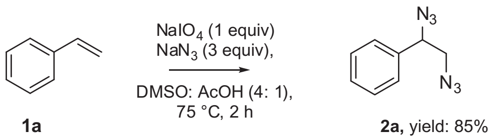
Entry	Aryl ketones (**3a**–**f**)	Geminal diazides (**4a**–**f**)	Yield[b] (%)
a	Propiophenone		96 (75)[c]
b	1,3-Diphenylpropan-1-one		94
c	3-(4-Methoxyphenyl)-1-phenylpropan-1-one		95
d	1-indanone		95
e	1-Tetralone		93 (70)[c] (28)[d]
f	2-Methyl-1-phenylpropan-1-one		35

Reaction conditions:
[a] Aryl ketone (5 mmol), NaIO$_4$ (5 mmol), NaN$_3$ (15 mmol), 20 ml of DMSO–AcOH (4:1), 75 °C, 2 h.
[b] Yield refers to isolated yield after column chromatographic purification.
[c] Yield corresponds to 1-phenyl-1-propanol and 1-tetralol as starting materials.
[d] Yield obtained using NaIO$_4$ (5 mmol) and NaN$_3$ (5 mmol).

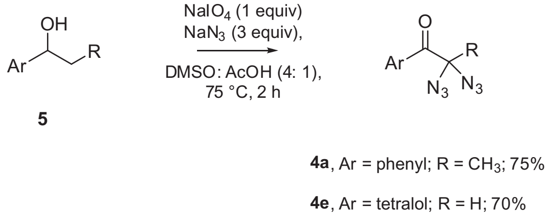
monitored by GC) even after carrying out the reaction for longer duration. The only product obtained in this case was 2,2-diazidoketone.

Benzylic alcohols, when treated under α,α-diazidation conditions (entries a & e), gave the corresponding α,α-diazido arylketones (**4a**[18] & **4e**) in good yields. This diazidation reaction probably occurred via the initial oxidation of benzylic alcohols (**5a** & **5e**) to form the corresponding aryl ketones, which then subsequently underwent diazidation at the α-position (Scheme 2).

The structures of 1,2-diazides **2a–o** and α,α-diazido arylketones **4a–f** were ascertained on the basis of spectroscopic data. The methine and methylene protons attached to azido groups in all



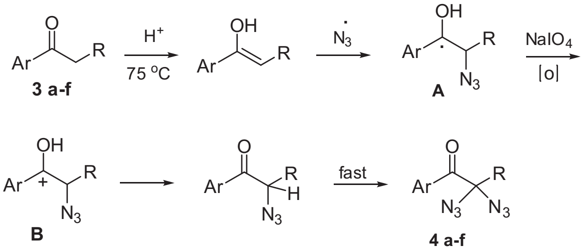
Scheme 1. $NaIO_4$-mediated 1,2-diazidation of styrene with NaN_3.



Scheme 2. $NaIO_4$-mediated α,α-diazidation of benzylic alcohols with NaN_3.

the 1,2-diazido compounds exhibited a typical signal in the range δ 2.36–4.02 in their ^{1}H NMR spectra whereas the carbons attached to azido groups have shown signal in the range δ 52.91–67.64 in their ^{13}C NMR spectra. In the case of α,α-diazido ketones (**4a–f**) quaternary carbon attached to diazido groups show δ values ranging from 80.1 to 85.7 in the ^{13}C NMR spectra. A strong characteristic IR absorption in the range 2076–2108 cm^{-1} for all the diazides confirms the presence of azide functionality. The formation of α,α-diazido aryl ketones **4a** was further confirmed by its conversion to an interesting di-triazole **6** using click chemistry reaction conditions[11] (Scheme 3).

Mechanistically, the reaction is believed to follow a radical pathway[10d] for both alkenes and aryl ketones. When the diazidation of styrene was carried out in the presence of catalytic amount of TEMPO, a dramatic decrease in the yield of diazido product **2a** (10%) was obtained, probably due to the radical quenching effect. It has been established that azide anion can be oxidized to the corresponding azide radical by Fe^{2+}–H_2O_2,[7] simple metal salts (Pb^{4+} or Mn^{3+})[12,5b] or electrochemically,[12,13] and can readily add to C=C to give vicinal diazido derivatives. In a similar manner, $NaIO_4$ oxidizes NaN_3 to generate an azide radical which then adds to alkenes to produce a more stable alkyl radical followed by its trapping with another azide radical resulting in the formation of 1,2-diazides **2a–o**. In the case of aryl ketones **3a–f**, the enol form of ketone reacts with azide radical to form a more stable benzylic radical species **A** which probably undergoes one electron oxidation with $NaIO_4$ to form a cationic species **B**. Expulsion of proton from **B** generates monoazidoketone which then subsequently undergoes second azidation at the α-CH position in a similar fashion to afford 1,1-diazides **4a–f**. In order to confirm the formation of monoazidoketone intermediate (Scheme 4), we carried out the diazidation of tetralone with 1 equiv each of NaN_3 and $NaIO_4$. However, the only product obtained was α,α-diazidoketone **4e** in 28% yield. Furthermore, when 2-azido-1-phenylpropan-1-one, was prepared separately from the corresponding 2-bromo-1-phenylpropan-1-one, and was subjected to diazidation conditions ($NaIO_4$, 1 equiv and NaN_3, 2 equiv), the only product obtained was 2,2-diazido-1-phenylpropan-1-one (20 min; 92% yield). This observation suggests that the rate of diazidation of monoazidoketone is much faster as compared to the diazidation of the parent aryl ketone.



Scheme 4. Proposed mechanism for the α,α-diazidation of aryl ketones.

In conclusion, we have developed a simple procedure[15] with $NaIO_4$–NaN_3 as a new combination for the 1,2-diazidation of alkenes and α,α-diazidation of aryl ketones, that provides direct and efficient entry to vicinal 1,2-diazidoalkanes and geminal 1,1-diazidoarylketones respectively in high yields. The transformation of aryl ketones and benzylic alcohols to the corresponding α,α-diazides is unprecedented and being reported for the first time. The geminal diazides (**4a–e**) are potential candidates to be used as future generation high energy materials for defense applications.[14]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.140.

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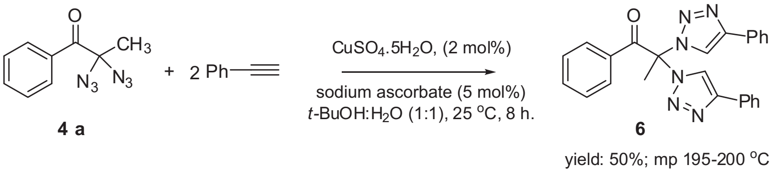

Scheme 3. Synthesis of ditriazole derivative **6**.

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15. *General experimental procedure for 1,2-diazidation of alkenes and α,α-diazidation of arylketones*: To a suspension of NaN_3 (15 mmol) and $NaIO_4$ (5 mmol) in 20 ml of DMSO–glacial AcOH (4:1) was added alkenes (5 mmol) or arylketone (5 mmol), as the case may be, and the reaction mixture was stirred at 75 °C for 2 h. It was monitored by TLC and then poured into water (100 ml) and extracted with EtOAc (3 × 50 ml). The combined organic layers were washed with saturated solution of aqueous $NaHCO_3$ (50 ml) followed by aqueous $Na_2S_2O_3$ (5%, 50 ml), dried over anhyd Na_2SO_4. Concentration of the organic layer gave crude diazides, which were purified by silica gel-packed column chromatography using hexane/ethyl acetate (19:1) as eluent to obtain pure 1,2-diazides **2a**–**o** or α,α-diazidoketones **4a**–**e**, respectively.
    Caution: All reactions employing NaN_3 and $NaIO_4$ were conducted in a hood behind a safety shield. However, we have not experienced any hazardous problem associated with NaN_3–$NaIO_4$ mixtures. Yet, care must be taken when dealing with mixture containing azides and oxidizing agents.
16. *5-(1,2-Diazidoethyl)benzo[1,3]dioxole (**2d**)*
    Yield: 90%; pale yellow liquid; IR (neat, cm^{-1}): 730, 933, 1102, 1247, 1444, 1504, 2100, 2902; ^1H NMR (200 MHz, $CDCl_3$): δ 3.31–350 (m, 2H), 4.53–4.60 (dd, *J* = 5.39, 7.79 Hz, 1H), 6.00 (s, 2H), 6.75–6.84 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.9, 65.3, 101.4, 107, 108.5, 120.8, 130.1, 148.3; GC–MS: *m*/*z* (% rel. intensity) 232 (M^+, 1) and 148 (100); Anal. Calcd for $C_9H_8N_6O_2$: C, 46.55; H, 3.47; N, 36.19; Found: C, 46.53; H, 3.47; N, 36.20.
17. *1,2-Diazido-1-(4-fluorophenyl)ethane (**2g**)*
    Yield: 89%; pale yellow liquid; IR (neat, cm^{-1}): 835, 1229, 1333, 1511, 1604, 2102; ^1H NMR (200 MHz, $CDCl_3$): δ 3.35–3.54 (m, 2H), 4.62–4.68 (dd, *J* = 5.6, 7.7 Hz, 1H), 7.06–7.16 (m, 2H), 7.27–7.37 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.9, 64.8, 115.9, 116.3, 128.7, 128.8, 132.2, 132.3, 160.4, 165.4; GC–MS: *m*/*z* (% rel. intensity) 206 (M^+, 4) and 95 (100); Anal. Calcd for $C_8H_7FN_6$: C, 46.60; H, 3.42; N, 40.70; Found: C, 46.58; H, 3.37; N, 40.76.
18. *2,2-Diazido-1-phenyl-propan-1-one (**4a**)*
    Yield: 96%; pale yellow liquid; IR (neat, cm^{-1}): 739, 1230, 1456, 1602, 1690, 2104, 2937; ^1H NMR (200 MHz, $CDCl_3$): δ 1.86 (s, 3H), 7.44–7.53 (m, 2H), 7.57–7.66 (m, 1H), 8.11 (t, *J* = 1.5 Hz, 1H), 8.14 (t, *J* = 1.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.0, 83.1, 128.3, 130.1, 132.5, 133.6, 191.7; Anal. Calcd for $C_9H_8N_6O$: C, 50.00; H, 3.73; N, 38.87; Found: C, 50.10; H, 3.68; N, 38.79.