An Efficient Oxidation of Element-Containing Propargyl Alcohols and Acetylenic γ-Diols by 2-Iodoxybenzoic Acid (IBX)

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Abstract: An efficient and convenient procedure for the oxidation of acetylenic alcohols and diols by *o*-iodoxybenzoic acid (IBX) is reported. Simple heating of the corresponding alcohol with a suspension of IBX in acetone or tetrahydrofuran leads to the silicon(germanium)-containing propynals or γ-hydroxypropynals in high yields.

Key words: propargyl alcohols, acetylenic diols, oxidation, IBX, propynals

Substituted α,β-acetylenic aldehydes are of great importance in modern organic chemistry. Propynals are applied in the synthesis of optically active acetylenic alcohols,[1] homoallylic amines and amino acids,[2] β-lactams, structural fragments of natural antibiotic malingolide,[3] ethynyl steroids, effective spasmolytics and antitumor drugs,[4] epoxydiynes, and key motifs of neocarzinostatin.[5] Propynals containing a hydroxy moiety in the γ-position to the carbonyl group, represent polyfunctional substrates for the design of diverse heterocyclic compounds.[6] It is known that the simplest γ-hydroxypropynal, generated in vivo by to enzymatic oxidation of but-2-yne-1,4-diol, participates in the irreversible inhibition of enzymes via the interaction of the aldehyde with the nucleophilic core of the enzymes.[7] The α-silicon- or germanium-containing groups stabilize acetylenic compounds and the products of their transformations, while subsequent heterolysis of the M–C_{sp} bond will lead to analogues with a terminal triple bond. Element-substituted propynals are used in the total synthesis of natural cytostatics, phorboxazoles[8] (inhibitors of thrombocytes aggregation), xemilofiban,[9] as well as for the preparation of 1*H*-1,2,3-triazolecarbaldehydes,[10] 3,4-dihydropyrimidin-2-ones,[11] [(trimethylsilyl)ethynyl]-4*H*-pyran-3,5-dicarbaldehyde,[12] imidazo[1,2-*a*]pyridine-3-carbaldehydes,[13] silicon(germanium)-containing ynimines and enynes,[14] substituted porphyrins,[15] and polyfunctional Baylis–Hillman adducts.[16]

One of the most widespread methods for the synthesis of propynals is by the oxidation of the corresponding acetylenic alcohols using different oxidants such as activated manganese dioxide,[17] chromium(VI) compounds,[18] dimethyl sulfoxide (Swern oxidation),[19] titanium(IV) chloride–triethylamine complex,[20] and molecular oxygen in the presence of an oxovanadium complex.[21] Activated manganese dioxide and pyridinium chlorochromate are the most commonly used reagents for this purpose.[18b]

Oxidation of primary/tertiary γ-diols **1a–e** by neutral manganese dioxide gives hydroxyaldehydes **2a–e** in 50–70% yields.[22] The disadvantages of this method are long reaction times and the requirement to use excess oxidant (from 5[22,23] to 26 equiv[24]) that can be accompanied by a decrease in the yield of the aldehyde due to absorption onto manganese dioxide. (Trialkylsilyl)- and (trialkylgermyl)acetylenic alcohols **1f,g** are effectively oxidized by pyridinium chlorochromate to afford the corresponding propynals **2f,g**.[25] However, 3-(trimethylsilyl)prop-2-ynal (**2g**) prepared by this method polymerizes during storage. We have shown that pyridinium chlorochromate is unsuitable for the preparation of γ-hydroxypropynals **2a–e** because of their strong resinification. Efforts to isolate aldehyde **2g** during the oxidation of 3-(trimethylsilyl)prop-2-yn-1-ol by potassium chromate/sulfuric acid under phase-transfer catalysis failed due to strong resinification.[26] This fact is indicative of the sensitivity of the acetylenic aldehydes **2a–g** to the reaction conditions. Therefore, a search for mild and effective oxidants seems to be an urgent synthetic challenge.

Over the last few decades, hypervalent iodine compounds such as Dess–Martin periodinane (DMP) and *o*-iodoxybenzoic acid (IBX) have been shown to have mild and selective properties and, thus, they have been used extensively for the oxidation of alcohols to carbonyl compounds.[27,28] For example, primary alcohols are transformed to aldehydes using IBX without overoxidation to acids,[29] amino alcohols are oxidized to the corresponding carbonyl derivatives without protection of the amino group, and sensitive heterocycles are not affected.[30,31] Compared to Dess–Martin periodinane, IBX is more readily available, it has moisture- and air-resistant properties, it can be generated in situ,[32] it does not cleave the C–C bond during the oxidation of 1,2-diols,[29] and it is easily recovered.[33] Moreover, although IBX only dissolves in dimethyl sulfoxide, it is possible to perform the oxidation of alcohols with IBX suspended in other solvents (THF,[30] MeCN, acetone, EtOAc,[34] aq acetone in presence of β-cyclodextrin[35]) thus avoiding tedious workup problems typical of dimethyl sulfoxide.

Various examples have been reported of the use of hypervalent iodine compounds for the oxidation of acetylenic

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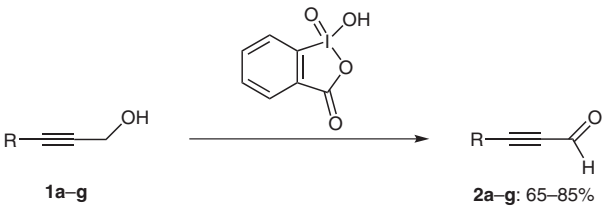
alcohols: but-2-yne-1,4-diol and propargyl alcohol by Dess–Martin periodinane with the thus generated aldehyde reacted with the Wittig reagent;[36] and secondary acetylenic alcohols[24] or chiral rhenium complexes of primary and secondary propynols[37] by the action of IBX solution in dimethyl sulfoxide at ambient temperature. However, the oxidation of acetylenic γ-diols and element-containing propargyl alcohols by IBX has not been studied yet.

Despite the high efficiency of IBX solution in dimethyl sulfoxide, its application for the oxidation of glycols **1a–e** is undesirable, since the relatively high hydrophilicity of aldehydes **2a–e** results in a considerable decrease in the yield when the reaction mixture is treated with water.

Therefore, we have investigated the efficiency of the oxidation of acetylenic γ-diols and element-containing propynols by IBX suspension in acetone or tetrahydrofuran. The IBX suspension in tetrahydrofuran has been successfully used for the first time for the oxidation of 2-hydroxy-2-phenylacetophenone [IBX (1.44 equiv), reflux],[30] while during the oxidation of piperonyl alcohol with IBX (3 equiv, reflux) with tetrahydrofuran as the solvent, oxidation of the tetrahydrofuran does not allow the target aldehyde to be isolated.[34]

The application of IBX (1.2 equiv) in tetrahydrofuran or acetone made possible the successfully oxidation of primary/tertiary γ-diols **1a–e** and trialkylsilyl(germyl)acetylenic alcohols **2f**,**g** under reflux for four hours (Scheme 1).



Scheme 1

The conversion of the alcohols is 90–99% (^{1}H NMR), while the isolated yields of aldehydes **2a–g** after distillation in vacuo are 65–85% (Table 1).

It has been pointed out that an increase of the reaction time (THF) up to 24 hours does not result in a rise in conversion. We have shown that the usage of almost equimolar amount of IBX (1.2 equiv) in the form of a suspension in tetrahydrofuran allows the oxidation of acetylenic alcohols and diols containing a primary hydroxy moiety in the α-position of the triple bond to be performed. Under the conditions studied, competitive oxidation of the solvent is not observed. The replacement of tetrahydrofuran by the less expensive solvent acetone enables the target aldehydes to be prepared with equal efficiency.

The decrease in yield of 4-hydroxy-4-phenylpent-2-ynal (**2e**) to 65% is caused by its high boiling point that causes resinification under distillation in vacuo. The lower yield of 3-(trimethylsilyl)prop-2-ynal (**2g**) as compared to germanium analogue **2f** is explained by product loss during removal of solvent from the reaction mixture owing to the high volatility of this aldehyde.

2-Iodosobenzoic acid filtered off from the reaction mixture has been reoxidized to IBX in 76% yield according to the literature procedure.[33] The regenerated IBX has been used repeatedly without decreasing the yield of the aldehydes.

It should be noted that propynals **2a–f** prepared by the method discussed, as well as by oxidation with activated manganese dioxide, are stable in long-term storage in a refrigerator.

In summary, we have shown the high efficiency of the application of IBX suspension in acetone or tetrahydrofuran for the oxidation of primary α-acetylenic alcohols and primary/tertiary γ-glycols to the corresponding propynals under mild conditions.

IR spectra were taken on a Bruker IFS-25 spectrometer (400–4000 cm^{-1}, thin film). ^{1}H (400.13 MHz) and ^{13}C NMR (101.62 MHz) spectra were recorded on a Bruker DPX-400 instrument with $CDCl_3$ as solvent and HMDS as internal standard. IBX was synthesized by

Table 1 Oxidation of Alcohols **1a–g** to Propynals **2a–g**

Alcohol	R	Conversion[a] (%)		Propynal	Isolated yield (%)	
		Acetone	THF		Acetone	THF
1a	$C(OH)Me_2$	97	95	**2a**	85	84
1b	C(OH)MeEt	95	92	**2b**	81	79
1c	C(OH)MePr	98	98	**2c**	82	83
1d	1-hydroxycyclohexyl	98	90	**2d**	80	76
1e	C(OH)MePh	97	96	**2e**	66	65
1f	$GeEt_3$	99	99	**2f**	85	82
1g	$SiMe_3$	98	97	**2g**	70	71

[a] ^{1}H NMR.

a literature method.[33] Compound **2e** is a new compound; aldehydes **2a**–**d** were previously characterized only by IR and ^{1}H NMR spectra.[22]

Propynals 2; General Procedure

Method A: A mixture of alcohol (35.1 mmol) and IBX (42.1 mmol) in THF (40 mL) was refluxed for 4 h with stirring. The mixture was filtered and the precipitate was washed with Et_2O (4 × 25 mL).The combined filtrates were evaporated and distilled in vacuo.

Method B: A mixture of alcohol (35.1 mmol) and IBX (42.1 mmol) in acetone (40 mL) was refluxed for 4 h with stirring. The mixture was filtered and the precipitate was washed with acetone (4 × 25 mL). The combined filtrates were evaporated and distilled in vacuo.

4-Hydroxy-4-methylpent-2-ynal (2a)

Yield: 84% (A), 85% (B); bp 56–58 °C/3.33 mbar; n_D^{20} 1.4708.

IR (film): 3400 (OH), 2205 (C≡C), 1670 cm^{-1} (C=O).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.57 [s, 6 H, $(CH_3)_2COH$], 9.22 (s, 1 H, CHO).

^{13}C NMR (101.62 MHz, $CDCl_3$): δ = 30.41 [$(CH_3)_2COH$], 65.10 [$(CH_3)_2COH$], 81.34 (≡*C*CHO), 100.16 (C*C*≡), 176.74 (C=O).

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.08; H, 7.13.

4-Hydroxy-4-methylhex-2-ynal (2b)

Yield: 79% (A), 81% (B); bp 67–68 °C/4 mbar; n_D^{20} 1.4726.

IR (film): 3380 (OH), 2215 (C≡C), 1675 cm^{-1} (C=O).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.05 (t, 3 H, CH_2CH_3), 1.53 (s, 3 H, CH_3COH), 1.76 (q, 2 H, CH_2CH_3), 2.59 (br s, 1 H, OH), 9.23 (s, 1 H, CHO).

^{13}C NMR (101.62 MHz, $CDCl_3$): δ = 8.89 (CH_3CH_2), 28.86 (CH_3COH), 35.99 (CH_3CH_2), 68.71 (CH_3COH), 82.77 (≡*C*CHO), 99.75 (C*C*≡), 176.59 (C=O).

Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.48; H, 7.90.

4-Hydroxy-4-methylhept-2-ynal (2c)

Yield: 83% (A), 82% (B); bp 70–71 °C/2.66 mbar; n_D^{20} 1.4708.

IR (film): 3390 (OH), 2210 (C≡C), 1670 cm^{-1} (C=O).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.97 (t, 3 H, $CH_2CH_2CH_3$), 1.52 (s, 3 H, CH_3COH), 1.61 (m, 2 H, $CH_2CH_2CH_3$), 1.73 (t, 2 H, $CH_2CH_2CH_3$), 2.38 (br s, 1 H, OH), 9.23 (s, 1 H, CHO).

^{13}C NMR (101.62 MHz, $CDCl_3$): δ = 14.14 ($CH_3CH_2CH_2$), 17.88 ($CH_3CH_2CH_2$), 28.98 (CH_3COH), 45.19 ($CH_3CH_2CH_2$), 68.34 (CH_3COH), 82.73 (≡*C*CHO), 99.69 (C*C*≡), 176.86 (C=O).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.48; H, 8.54.

3-(1-Hydroxycyclohexyl)prop-2-ynal (2d)

Yield: 76% (A), 80% (B); bp 106–108 °C/3.33 mbar; n_D^{20} 1.5112.

IR (film): 3390 (OH), 2200 (C≡C), 1665 cm^{-1} (C=O).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.28 (m, 2 H, γ-CH_2), 1.51–1.71 (m, 8 H, α,β-CH_2), 2.29 (br s, 1 H, OH), 9.24 (s, 1 H, CHO).

^{13}C NMR (101.62 MHz, $CDCl_3$): δ = 22.88 (γ-C), 24.93 (β-C), 39.11 (α-C), 67.99 (COH), 82.73 (≡*C*CHO), 99.69 (C*C*≡), 176.65 (C=O).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 69.88; H, 7.84.

4-Hydroxy-4-phenylpent-2-ynal (2e)

Yield 65% (A), 66% (B); bp 138–142 °C/2.66 mbar; n_D^{20} 1.6070.

IR (film): 3400 (OH), 2215 (C≡C), 1675 cm^{-1} (C=O).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.77 (s, 3 H, CH_3COH), 3.96 (br s, 1 H, OH), 7.11–7.54 (m, 5 H, Ph), 9.15 (s, 1 H, CHO).

^{13}C NMR (101.62 MHz, $CDCl_3$): δ = 32.42 (CH_3COH), 69.93 (CH_3COH), 83.60 (≡*C*CHO), 98.98 (C*C*≡), 124.85–128.57 (Ph), 176.89 (C=O).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.78. Found: C, 75.67; H, 5.69.

3-(Triethylgermyl)prop-2-ynal (2f)

Yield: 82% (A), 85% (B); bp 81–82 °C/8 mbar; n_D^{20} 1.4861.

IR (film): 2145 (C≡C), 1670 cm^{-1} (C=O).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.94 (q, 6 H, CH_2CH_3), 1.13 (t, 9 H, CH_2CH_3), 9.11 (s, 1 H, CHO).

^{13}C NMR (101.62 MHz, $CDCl_3$): δ = 5.66 (CH_2CH_3), 9.00 (CH_2CH_3), 103.40 (GeC≡), 104.50 (≡*C*C), 176.10 (C=O).

Anal. Calcd for $C_9H_{16}GeO$: C, 50.79; H, 7.57; Ge, 34.12. Found: C, 50.57; H, 7.39; Ge, 33.88.

3-(Trimethylsilyl)prop-2-ynal (2g)

Yield: 71% (A), 70% (B); bp 53–55 °C/40 mbar; n_D^{20} 1.4448.

IR (film): 850, 2165 (C≡C), 1680 (C=O), 1260 cm^{-1} (Si–C).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.18 (s, 9 H, CH_3), 9.10 (s, 1 H, CHO).

^{13}C NMR (101.62 MHz, $CDCl_3$): δ = –1.80 (CH_3), 102.11 (SiC≡), 102.69 (≡*C*C), 176.47 (C=O).

Anal. Calcd for $C_6H_{10}OSi$: C, 57.09; H, 7.98; Si, 22.25. Found: C, 56.94; H, 7.79; Si, 22.01.

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