Stereoselective Synthesis of 2-Functionalized 1-Bromo-1-iodo-1-alkenes by Electrophilic Iodination of 1-Bromo-1-alkynes

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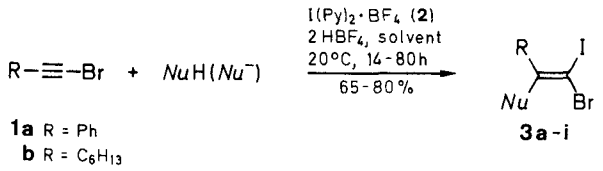
1-Bromo-1-alkynes **1** react with bis(pyridine)iodine(I) tetrafluoroborate **(2)** and nucleophiles (AcOH, HCO_2H, Cl^-, Br^-, I^-) to give in a stereoselective addition 2-functionalized 1-bromo-1-iodo-1-alkenes **3**

The one-carbon homologation of carbonyl compounds in a Wittig-like reaction has been employed to prepare *gem*-dibromo-[1] and *gem*-diiodovinyl[2] derivatives, but there is not a general method to synthesize *gem*-iodobromoalkenes. The bromine-iodine exchange (from *gem*-dibromo olefins) with a mixture of copper(I) iodide and potassium iodide in hexamethylphosphoric triamide gives the corresponding diiodo compound,[3] and with sodium iodide in acetone a mixture of iodobromovinyl and disubstituted product.[4]

Other methodology consists of the electrophilic addition to 1-halo-1-alkynes. In this way, the reactions of bromine or iodine,[5] hydrogen bromide or iodide,[6] and iodine monobromide[6] give the corresponding bromoiodoalkenes, but in some processes mixtures of several products are obtained.[6] The addition of iodine azide[7] and iodine isocyanate[8] to 1-bromo-2-phenylethyne lead to unstable and non-isolable products. The scope of these methods is very poor and consequently are not valuable for a general preparation of 2-functionalized bromoiodoalkenes.

We have recently reported, the first synthesis of 2-functionalized 1,1-diodo-1-alkenes,[9] and their ulterior transformation into a new class of organometallic compounds,[9,10] and also the preparation of 2-functionalized 1-chloro-1-iodo-1-alkenes.[11] We describe here a general method to prepare 2-functionalized 1-bromo-1-iodo-1-alkenes.

The reaction of a 1-bromo-1-alkyne **1**[12] with bis(pyridine)iodine(I) tetrafluoroborate **(2)**, in the presence of different nucleophiles and two equivalents of tetrafluoroboric acid (54% ethereal solution), yielded a 2-functionalized 1-bromo-1-iodo-1-alkene **3**, as a single regio- and stereoisomer (Scheme 1 and Table 1).



3	R	*Nu*	3	R	*Nu*
a	Ph	OAc	**f**	C_6H_{13}	OCHO
b	Ph	OCHO	**g**	C_6H_{13}	Cl
c	Ph	Cl	**h**	C_6H_{13}	Br
d	Ph	Br	**i**	C_6H_{13}	I
e	C_6H_{13}	OAc			

Scheme 1

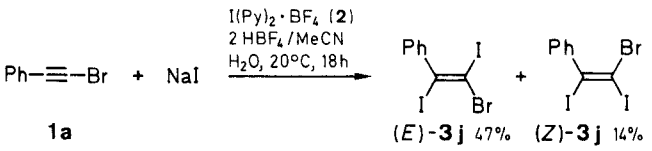
A mixture of stereoisomers was obtained only when 1-bromo-1-phenylethyne **(1a)** was used as the starting material and sodium iodide as the nucleophile (Scheme 2 and Table 1).

The reactions take place at room temperature in a similar way to previously reported iodofunctionalizations of other alkynes.[9,11,13] After usual work-up

Table 1. Experimental Data for the Preparation of **3a–j**

Product	Nucleophile	Solvent	Reaction Time (h)	Yield (%)[a]	Molecular Formula[b] or Lit. mp (°C)
3a[c]	AcOH	$AcOH/CH_2Cl_2$ (2:1)	14	79	$C_{10}H_8BrIO_2$ (367.0)
3b[c]	HCO_2H[d]	HCO_2H/CH_2Cl_2 (2:1)	14	80	$C_9H_6BrIO_2$ (353.0)
3c	LiCl[e]	$MeCN/H_2O$ (5:1)	80	65	C_8H_5BrClI (343.4)
3d	LiBr[e]	$MeCN/H_2O$ (5:1)	70	73	$C_8H_5Br_2I$ (387.8)
3e[c]	AcOH	$AcOH/CH_2Cl_2$ (2:1)	14	71	$C_{10}H_{16}BrIO_2$ (375.0)
3f[c]	HCO_2H[d]	HCO_2H/CH_2Cl_2 (2:1)	14	80	$C_9H_{14}BrIO_2$ (361.0)
3g	LiCl[e]	$MeCN/H_2O$ (5:1)	80	79	$C_8H_{13}BrClI$ (351.5)
3h	LiBr[e]	$MeCN/H_2O$ (5:1)	70	75	$C_8H_{13}Br_2I$ (395.9)
3i	NaI[e]	$MeCN/H_2O$ (5:1)	20	73	$C_8H_{13}BrI_2$ (442.9)
3j[f]	NaI[e]	$MeCN/H_2O$ (5:1)	18	61 (3.3:1)[g]	62–62.5[h]

[a] Yield of isolated product, relative to starting **2** and not optimized. The products were purified by passing through a short column of silica gel and eluting with hexane.
[b] Satisfactory microanalyses obtained: C ±0.31, H ±0.20.
[c] The product could not be purified because of decomposition. Elemental analyses were not assayed.
[d] Aqueous 85% solution.
[e] Mole ratio *Nu*/**2** = 10:1.
[f] (*E*)- and (*Z*)-isomers could not be separated.
[g] (*E*)-(*Z*) ratio, determined by ^{13}C NMR spectroscopy of the reaction mixture.
[h] α,β-Diiodo-β-bromostyrene was described in Ref. 8 without specification of its stereochemistry.



Scheme 2

procedure (see experimental), compounds **3** were obtained in good yields with more than 90% purity (determined by GC analysis), as the residue of solvent evaporation at reduced pressure. The reaction products were purified by eluting with hexane, in a short column packed with silica gel to eliminate the unreacted starting alkyne.

1-Bromo-1-iodo-1-alkenes **3** were analyzed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry (Table 2). Regiochemistry was determined based on the ^{13}C NMR chemical shift of vinylic carbon that bears both the iodine and bromine atoms. These carbons appear as small singlets between values of $\delta = 61.3$ and 45.5. The polar effect of the bromine atom linked to the triple bond induces a regiospecific addition of iodine to C-1.

Almost in all the cases, only a single stereoisomer was observed, the (*E*)-isomer, in agreement with the previously proposed addition mechanism through a vinyleneiodonium ion.[13] In addition, when the steric hindrance of the alkyne substituent was increased (R = Ph),[14] some syn-addition occured in the case of the strongest nucleophile (I^-), leading to mixture of stereoisomers [(*E*)-**3j**: (*Z*)-**3j** = 3.3:1, Scheme 2]. The assignments of configuration, either (*E*)- or (*Z*)-isomer, is based on the ^{13}C NMR chemical shift of the phenylic ipso-carbon. The observed effect of an iodine atom in cis is to displace the ipso signal to lower field. On the contrary, bromine causes identical shift in cis or trans position.[15] Similar results were observed with 1-chloro-1-alkynes (ratio *E*:*Z* for 1-chloro-2-phenylethyne and sodium iodide = 4.5:1),[11] where the major proportion of (*E*)-isomer obtained may be explained by the less steric hindrance requirement of chlorine atom.[14]

Following this procedure we have synthesized several 1-bromo-1-iodo-1-alkenes **3** with a function in 2-position (chloro, bromo, iodo, or acyloxy). These compounds are new, and present a high synthetic potential. Some of them feature three different halo atoms (**3c** and **3g**) attached to the vinylic carbons with well defined regio- and stereochemistry.

^1H and ^{13}C NMR spectra were recorded on a Varian FT-80 A or a Bruker AC-300 spectrometers in $CDCl_3$ and TMS as internal standard. Mass spectra were run on a HP 5987 A apparatus. Elemental analyses were performed on a Perkin-Elmer 240 Elemental Analyzer. GC analyses were carried out on a Varian Vista

Table 2. Spectral Data of Compounds **3** Prepared

Compound	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ	MS (70 eV) *m/z* (%)
3a	2.1 (s, 3H), 7.3–7.5 (m, 5H)	21.0 (CH_3), 49.0 (C=CBrI), 129.2, 130.3, 130.9, 135.9, (C_{arom}), 152.1 (AcOC=C), 167.9 (CO)	368 [$(M+2)^+$, 2], 366 (M^+, 2), 326 (95), 324 (100), 248 (31), 246 (32), 241 (18), 239 (18), 118 (13), 105 (19)
3b	7.3–7.5 (m, 5H), 8.0 (s, 1H)	50.1 (C=CBrI), 129.7, 130.5, 131.3, 135.4 (C_{arom}), 151.0 (C=COCHO), 158.0 (CHO)	354 [$(M+2)^+$, 11], 352 (M^+, 11), 326 (69), 324 (70), 248 (99), 246 (100), 327 (34), 325 (34), 118 (51)
3c	7.3 (br s)	53.8 (C=CBrI), 129.5, 129.8, 130.5, 136.9 (C_{arom}), 140.4 (ClC=C)	346 [$(M+4)^+$, 8], 344 [$(M+2)^+$, 30], 342 (M^+, 24), 219 (4), 217 (14), 215 (10), 182 (15), 180 (15), 138 (32), 136 (100), 127 (19), 101 (30)
3d	7.2 (br s)	55.2 (C=CBrI), 127.7, 130.2, 130.4, 131.1 (C_{arom}), 143.8 (BrC=C)	390 [$(M+4)^+$, 33], 388 [$(M+2)^+$, 61], 386 (M^+, 33), 309 (54), 307 (55), 261 (4), 228 (5), 182 (90), 180 (100), 127 (10), 101 (37)
3e	0.8 (t, 3H, *J* = 7), 1.1–1.5 (m, 8H), 2.0 (s, 3H), 2.4 (t, 2H, *J* = 6.5)	13.8 (CH_3), 20.0 (MeCO), 22.1, 25.9, 28.2, 31.1, 35.0 [$(CH_2)_5$], 45.5 (C=CBrI), 153.5 (AcOC=C), 167.5 (CO)	376 [$(M+2)^+$, 2], 374 (M^+, 2), 334 (7), 332 (7), 248 (3), 246 (3), 137 (20), 135 (22)
3f	0.8 (t, 3H, *J* = 7), 1.0–1.6 (m, 8H), 2.5 (t, 2H, *J* = 6.7), 7.9 (s, 1H)	14.4 (CH_3), 22.8, 26.4, 28.9, 31.9, 35.7 [$(CH_2)_5$], 46.6 (C=CBrI), 154.0 (C=COCHO), 158.0 (CHO)	362 [$(M+2)^+$, 16], 360 (M^+, 16), 334 (6), 332 (6), 264 (10), 262 (10), 248 (9), 246 (7), 153 (16), 137 (100), 135 (92), 125 (29), 107 (36)
3g	0.8 (t, 3H, *J* = 7), 1.0–1.5 (m, 8H), 2.5 (t, 2H, *J* = 6.5)	15.2 (CH_3), 23.6, 28.3, 29.2, 32.8, 43.0 [$(CH_2)_5$], 50.9, (C=CBrI), 140.7 (ClC=C)	354 [$(M+4)^+$, 1], 352 [$(M+2)^+$, 3], 350 (M^+, 3), 260 (6), 258 (6), 155 (14), 153 (13), 127 (5), 107 (44)
3h	0.8 (t, 3H, *J* = 7), 1.0–1.7 (m, 8H), 2.6 (t, 2H, *J* = 6.8)	14.8 (CH_3), 23.0, 28.5, 28.8, 32.1, 45.6 [$(CH_2)_5$], 51.0, (C=CBrI), 132.1 (BrC=C)	398 [$(M+4)^+$, 14], 396 [$(M+2)^+$, 32], 394 (M^+, 16), 260 (20), 258 (19), 247 (31), 245 (32), 201 (11), 199 (26), 197 (15), 147 (29), 145 (19), 119 (38), 117 (44), 109 (14), 108 (44), 107 (100)
3i	0.8 (t, H, *J* = 7), 1.0–1.5 (m, 8H), 2.5 (t, 2H, *J* = 6.7)	13.8 (CH_3), 22.2, 27.7, 28.2, 31.2, 50.0 [$(CH_2)_5$], 52.7 (C=CBrI), 111.9 (IC=C)	444 [$(M+2)^+$, 35], 442 (M^+, 36), 373 (7), 371 (7), 247 (96), 245 (98), 165 (19), 119 (46), 117 (41), 109 (33), 108 (81), 107 (100)
3j	7.2–7.3 (m)[a]	57.3 (C=CBrI), 104.9 (IC=C), 127.6, 128.4, 128.6, 146.4 (C_{arom})[b] 61.3 (C=CBrI), 111.1 (IC=C), 127.4, 128.2, 128.5, 143.6 (C_{arom})[c]	436 [$(M+2)^+$, 13], 434 (M^+, 11), 309 (43), 307 (46), 228 (28), 182 (100), 180 (97), 127 (47), 101 (63)[a]

[a] Spectral data of a mixture (*E*) + (*Z*)-isomers.
[b] ^{13}C NMR data of (*E*)-**3j**.
[c] ^{13}C NMR data of (*Z*)-**3j**.

6000 gas chromatograph using a OV-101 column. Reagents and solvents were commercial grades (Merck and Aldrich). Compound **2** was prepared in accordance with the previously described method,[13] and 1-bromo-1-alkynes **1** were synthesized by bromination of metal alkynides with NBS.[12]

(*E*)-1-Bromo-1-iodo-1-alkenes 3; General Procedure:

HBF_4 (10 mmol, 1.40 mL of a 54% ethereal solution), bis(pyridine)iodine(I) tetrafluoroborate (**2**; 5 mmol, 1.86 g), and the corresponding alkyne **1** (5 mmol) were added to a solution of the nucleophile in the appropriate solvent (20 mL) (see Table 1) at r.t. After stirring, the red solution was poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organic layer was washed with 5% aq $Na_2S_2O_3$ (25 mL) (and twice with 25 mL of 5% aq $NaHCO_3$ when then nucleophile is AcO^- or HCO_2^-), dried (Na_2SO_4) and evaporated at reduced pressure. The crude product was purified by eluting with hexane in a short column packed with silica gel to give **3** as a dark oil. Attempts to distill compound **3** in vacuo failed due to its decomposition (Tables 1 and 2).

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