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Formations of Mixed β,β-Dihaloenals from Halogenated Secondary Alkynols

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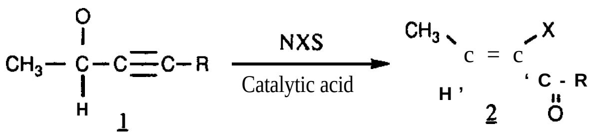
Abstract. Iodine and Koser's reagent have been used in stoichiometric amounts to convert 3-bromo-1-phenylpropynol to (Z)-3-bromo-3-iodo-2-phenylpropenal in high yield. The latter is a major component of reaction mixtures of 3-iodo-1-phenylpropynol and bromine with Koser's reagent.

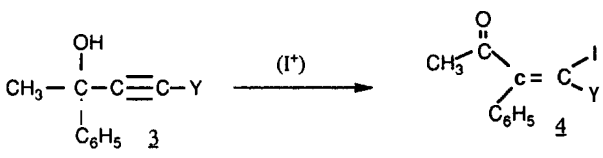
Recently we reported the conversions of secondary alkynols (1) to a-iodoenones (2) with N-iodosuccinimide (NIS) and catalytic quantities of Lewis acids such as [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent). Bromoenones were formed in an analogous manner with N-bromosuccinimide (NBS) and catalytic silver tetrafluoroborate.[1]



a, R = C_2H_5
b, R = C_6H_5

a, R = C_2H_5, X = I or Br
b, R = C_6H_5, X = I or Br

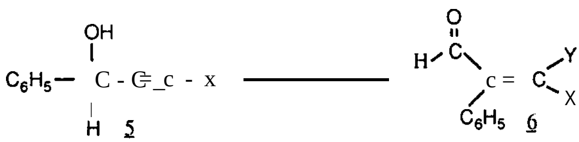
This "Halo-Meyer-Schuster" reaction stands in contrast with the conversions of tertiary alkynols to β-iodoenones.[2,3] With stoichiometric or greater amounts of iodine and iodic acid 3a-c were converted to 4a-c.[4]



a, Y = C_6H_5; b, Y = H; c, Y = I: d, Y = Br

The conversion of 3c to 4c was lately modified to give mixed β,β-dihaloenones (such as the conversion with I_2 and HTIB of 3d to 4d), whose stereospecific formations render them excellent templates for exchanges of the halogens by transition metal-catalyzed coupling techniques.[5] A similar conversion to mixed β,β-dihaloenals would expand the utility of such methodologies, but the starting materials would be secondary alkynols, which seem to prefer the "Halo-Meyer-Schuster" pathways.

We now report such is not the case if the halogenated secondary alkynols are the starting materials. The mechanistic guideline for this direction would be that halonium attack at the a-position required of a "Halo-Meyer-Schuster" process would lead to a vinyl cation destabilized by a halogen at the P-position. A more stable cation would be formed by attack at the P-position and would be the terminus of a group shift from the alcohol-bearing carbon. In particular, 3-bromo-1-phenylpropynol (5a) has been converted to (Z)-3-bromo-3-iodo-2-phenylpropenal (6a) by means of iodine and HTIB in stoichiometric quantities.

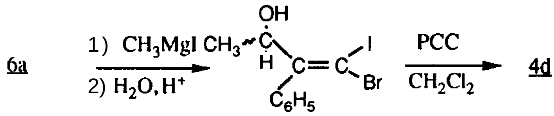


a, X = Br; b, X = 1 a, X = Br, Y = I; b, X = I, Y= Br

When 5a (1 mmol) was treated with iodine (1 mmol) and HTIB (1 mmol) in acetonitrile (10ml) at room temperature overnight, mixed dihaloenal 6a was formed in 96% yield." When the quantities of iodine and HTIB were reduced to one-half molar, the yield was 7 1%. The uses of NIS and catalytic quantities of HTIB with 5a in acetonitrile or methanol were ineffective. The catalytic presence of p-toluenesulfonic acid (TsOH) with NIS in acetonitrile, however, led to the conversion (65%) of 5a, but the selectivity to 6a was 71%. The results with different iodinating systems reflect the electron withdrawing effect of the bromine on the alkyne and the subsequent deactivation of any intermediate vinyl cations.

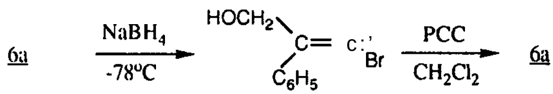
The spectral data for the clear oil 6a was as follows, IR (neat) 3030 (m), 2850 (m), 2730 (w), 1690 (s), 1600 (m), 1270 (s), 1090 (s) cm-t; ^{1}H-NMR (CDC13) δ 7.16 (m, 2H), 7.45 (m, 3H), 9.86 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 80.57 (C3), 128.49, 128.76, 128.82, 131.19, 135.07, 147.60, 152.14 (C2), 192.66 (Cl); mass spectrum, m/e (rel. intensity) 336/338 (6, M^+), 209/211 (3, M+-I), 181/183 (1 1, M+-I-CO), 180/182 (11, $C_6H_5C_2Br$), 127 (21, I), 102 (100, $C_6H_5C_2H$); anal. C,H.

An assignment of stereochemistry was based on a conversion of 6a to 4d by means of a Grignard reaction followed by an oxidation with pyridinium chlorochromate (PCC).



7

In order to rule out an isomerization in the oxidation step in the conversion of 7 to 4d, the haloenal was reduced at low temperature with $NaBH_4$ to obtain allylic alcohol 8 which was converted back to 6a with PCC/CH_2Cl_2.



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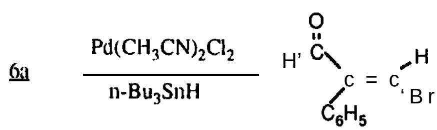
The intermediates 7 and 8 were not isolated but were characterized by GC/MS: 7 m/e (tel. int.) 354/352 (M+, 3), 227/225 (M-I, 3), 182/180 ($C_6H_5C_2Br$, 6), 127 (1, 13), 102 (33), 43 (100); 8 m/e (rel. int.) 340/338 (M+, 18), 214/212 (M-I, 16), 102 (100). The products of the PCC oxidation of 7 and 8 had the same GC/MS, ^1H NMR and IR as authentic samples.

Further evidence for the assigned stereochemistry of 6a stemmed from a reaction with $Pd(CH_3CN)_2Cl_2$ and Bu_3SnH that exchanged the vinyl iodine atom with a hydrogen atom.



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Compound 9 was isolated by silica gel chromatography: ^1H NMR ($CDCl_3$) δ 7.30 (m, 2H), 7.45 (m, 3H), 7.70 (s, 1H), 9.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 128.66, 129.41, 129.45, 130.28, 130.51, 132.51, 134.30, 134.35, 190.59; IR (nujol) 1706 (s), 1603 (m), 1495 (m), 1328 (s), 1172 (m), 1064 (s), 1020 (m), 809 (m), 772 (m), 716 (s) cm^{-1}. The appearance of the vinyl singlet at 7.70 ppm is particularly significant. It indictaes that the proton is syn to the carbonyl according to the studies of Piers on a variety of cyclic and acyclic enones.[7] In general, for haloenones protons syn to carbonyl had resonances between 7.35 and 7.70 ppm, whereas those that were anti had values between 6.28 and 6.96 ppm.

The starting material **5a** was prepared from I-phenylpropynol and NBS in acetone stirred over catalytic amounts of silver nitrate.8 This general procedure was used to prepare the iodinated analogue **5b** from 1-phenylpropynol and $NIS/AgNO_3$ as well.

Compound **5b** was treated with NBS and catalytic amounts of HTIB or TsOH in CH_3CN or methanol to no avail. The addition of Br_2 ond HTIB in stoichiometric quantities in acetonitrile gave a mixture of six products. With the use of half molar amounts of bromine and HTIB with **5b** three major components other than the artifactual iodobenzene were present. They were identified by GC/MS to be the following: **5a** (46%), **6a** (22%) and 3,3-diiodo-2-phenylpropenal (27%). None of the anticipated (E)-isomeric **6b** was detected.

This finding is consonant with the results of the mixed dihaloenone system wherein the principal shifted product of the iodinated alkynol was the Z-isomer rather than the (E)-isomer. Nonetheless, so long as the Z-isomer is formed in high yield stereospecifically, it would serve as a valuable synthetic template for vinyl halide exchange processes. The order of exchange allows flexibility in the selection of synthetic targets.9

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6) Work-up procedures consisted of addition of reaction mixture to water and extraction with ether. The ether layer was washed with 5% sodium thiosulfate and water. After drying over $MgSO_4$ and solvent evaporation any residue was taken up in CH_2Cl_2/CCL_4 and passed through a short column of silica gel to remove the iodobenzene formed from HTIB. Qualitative analyses were carried out with a GC/MS (Hewlett - Packard 5992, OV- 1, 0.25mm x 15m); quantitative analyses with a GC (Perkin-Elmer Sigma 3B, methyl silicone, 0.25mm x 50m).
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