

BROMO[3]CUMULENES AS PRECURSORS TO HALOENYNES

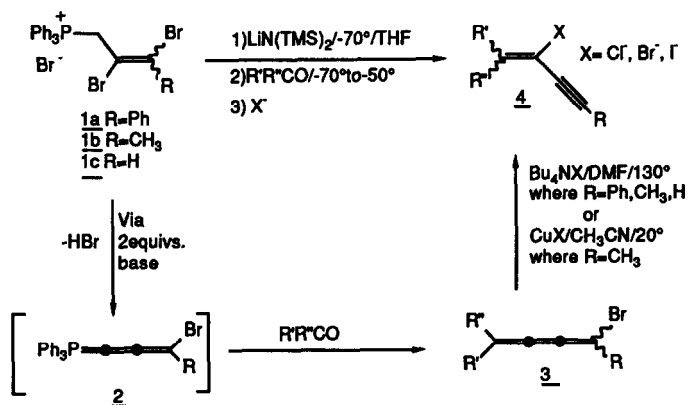
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Summary: A regioselective S_N2' synthesis of haloenynes starting from bromo[3]cumulenes is reported.

Halo[3]cumulenes are a relatively new group of highly unsaturated compounds. Their preparation originates primarily from two sources: the halogenation of 1,3-diyne⁽¹⁾, or perhaps more conveniently, via Wittig phosphacumulene methodology⁽²⁾. It is of interest to explore the synthetic utilization of these halo[3]cumulenes and recently we reported an unsymmetrical 1,3-diyne synthesis from trisubstituted bromo[3]cumulenes⁽³⁾. In this report, it is shown that haloenynes are produced in a novel regioselective halide displacement of suitably substituted bromo[3]cumulene precursors (Scheme 1). Haloenynes of this type are rare in the literature⁽⁴⁾, yet their use in synthesis holds considerable potential.

SCHEME 1



The synthesis involves an initial low temperature Wittig synthesis of the bromo[3]cumulene 3 from any of the allylic phosphonium salts 1a-1c and the requisite ketone, probably via the phosphacumulene ylid 2.

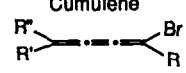
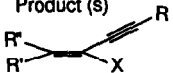
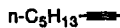
The intermediates with general structure 3, though sensitive to air, can be isolated and characterized⁽⁵⁾. Those synthesized (R = Ph, CH₃, H) underwent regioselective halide substitution to form the corresponding enynes with tetraalkylammonium salts (I⁻, Br⁻, Cl⁻) in hot DMF. Those haloenynes 4 formed usually are more stable than their butatriene precursors. Cuprous halides (I⁻ or Br⁻) on the other hand, effected substitutions of comparable yields only with cumulenes 3 derived from 1b (R = CH₃). In the other cases

(R = H, Ph) only low yields of product 4 were detected mixed with other uncharacterized side products⁽⁶⁾.

In essence, the overall transformation formally represents a S_N2' displacement. There are some reports involving this reaction type in allenic systems with organocuprate reagents⁽⁷⁾ and a single example utilizing 1,2,3-butatriene ethers⁽⁸⁾.

Those haloenyne synthesized by this procedure are presented in Table 1. A general overview shows that cumulenes prepared from all three phosphonium salts 1a-1c formed haloenyne mixtures on reaction with any of the tetraalkylammonium halide sources used (*i.e.* entries a, d and h). Increasing the tetra-alkylammonium iodide concentration had a commensurate effect on the iodide to bromide ratio as seen for entries a, b and c. On scaling the iodide concentration from 2 to 10 equivalents the iodoenyne to bromoenyne product ratio rose from 10 to 47.

TABLE 1

Entry	Cumulene 	Halide ^a (equivalents)	Conditions	Isolated Yield ^b	Product (s) 	Ratio ^c
a	R=H, R', R'' = (CH ₂) ₅ .	Bu ₄ Nl (2)	DMF/130° 1.75hrs.	62%	R=H, R', R''=(CH ₂) ₅ , X=I ; R=H, R', R''=(CH ₂) ₅ , X=Br	I/Br=10
b	R=H, R', R'' = (CH ₂) ₅	Bu ₄ Nl (5)	DMF/130° 1hr.	64%	R=H, R', R''=(CH ₂) ₅ , X=I ; R=H, R', R''=(CH ₂) ₅ , X=Br	I/Br=22
c	R=H, R', R'' = (CH ₂) ₅	Bu ₄ Nl (10)	DMF/130° 40min.	62%	R=H, R', R''=(CH ₂) ₅ , X=I ; R=H, R', R''=(CH ₂) ₅ , X=Br	I/Br=47
d	R=H, R', R'' = (CH ₂) ₅	BzNEt ₃ Cl (5)	DMF/130° 1.75hrs.	52%	R=H, R', R''=(CH ₂) ₅ , X=Cl ; R=H, R', R''=(CH ₂) ₅ , X=Br	Cl/Br=14
e	R=CH ₃ , R', R'' = (CH ₂) ₅	Bu ₄ NBr (5)	DMF/130° 2hr.	54%	R=CH ₃ , R', R'' = (CH ₂) ₅ , X=Br	
f	R=CH ₃ , R', R'' = (CH ₂) ₅	CuI (5)	CH ₃ CN/20° 18hrs.	57%	R=CH ₃ , R', R'' = (CH ₂) ₅ , X=I ; R=CH ₃ , R', R'' = (CH ₂) ₅ , X=Br	I/Br=1.4
g	R, R' = CH ₃ R'' = CH ₂ CH ₂ C=C(CH ₃) ₂	CuBr (2.5)	CH ₃ CN/20° 14hrs.	58%	R, R' = CH ₃ , X=Br R'' = CH ₂ CH ₂ C=C(CH ₃) ₂	1:1' E/Z
h	R=Ph, R', R'' = (CH ₂) ₅	Bu ₄ Nl (5)	DMF/130° 0.75hr.	58%	R=Ph, R', R'' = (CH ₂) ₅ , X=I ; R=Ph, R', R'' = (CH ₂) ₅ , X=Br	I/Br=18
i	R, =CH ₃ , R' = H R'' = n-C ₅ H ₁₃	CuI (5)	CH ₃ CN/20° 18hrs.	38%	R=CH ₃ , R' = H, R'' = n-C ₅ H ₁₃ , X=I R=CH ₃ , R' = H, R'' = n-C ₅ H ₁₃ , X=Br n-C ₅ H ₁₃  CH ₃	I/Br/Diyne= 1:1:1.4

a) Equivalents are based on the phosphonium salt. b) all isolated yields are unoptimized. c) Ratios were determined by vapor phase chromatography of the purified product mixtures. Isomeric mixtures were determined using a Hewlett-Packard 5890 gas chromatograph interfaced to a Finnegan MAT 710 ion-trap detector; 30 m x .25 mm ID column/0.25 m DB-5; 10°C/min to 220°.

The chemoselectivity exhibited by the cuprous halides is markedly less than that shown by the tetraalkylammonium salts. A 22:1 ratio of iodide to bromide is seen in entry b, whereas the cuprous iodide manifests a ratio slightly better than parity in entry f. This may be explained, in part, since the cuprous iodide reaction is heterogeneous. Thus, the effective iodide concentration in solution is much lower (than 5 equivalents) and most likely comparable to that of the eliminated bromide ion.

Despite its poorer nucleophilic character relative to the other salts, excess benzyltrimethylammonium chloride produced a 14:1 ratio of the chloro- to bromoenyne in fair yield (entry d). The corresponding fluoride salt gave uncharacterized products only⁽⁹⁾.

The bromo[3]cumulene 3 originating from hexanal (entry i) on reaction with CuI gave significant amounts of the dehydrohalogenation product, 1,4-diphenylbutadiyne, as contaminant which detracts from the synthetic utility of aldehydes in this method⁽¹⁰⁾.

Since the Wittig synthesis of the bromo[3]cumulenes 3 is not stereospecific (from unsymmetrical ketones) product mixtures consisting of E and Z haloenyne are realized from this approach. As expected, the bromoenyne in entry g (from 6-methyl-5-hepten-2-one) comprised a preparatively inseparable mixture of E and Z isomers (ratio=1).

Studies directed towards expanding the scope of this novel S_N2' reaction continue.

General Procedure for Haloenyne Synthesis Using Tetra-
alkylammonium Halides and Cuprous Halides: Preparation of
Cyclohexane (1-bromo-2-butynylidene), Entry e Table 1

The phosphonium salt 1b (3.50 g, 6 mmol) was suspended in 25 ml THF under an argon atmosphere at -70°C. To this was added lithium bis(trimethylsilyl)amide (12 mmol, as a 1M THF solution) over a 10 min. period. The resultant ylid solution was stirred 20 minutes. Cyclohexanone (0.81 g, 8.2 mmol) was rapidly added followed by 1 hr. stirring and gradual temperature increase to -50°C. The intermediate bromo[3]cumulene 3 [R = CH₃, R', R" = (CH₂)₅] was isolated crude by dilution with 150 ml Et₂O followed by filtration through a column of Florisil. Removal of most of the solvent preceded the addition of DMF (30 ml) and n-Bu₄NBr (9.7 g, 30 mmol). This solution was degassed with argon and then heated at 130°C under an argon atmosphere. After 1 hr. TLC (hexane, silica gel plates) indicated completion of the reaction. Product isolation was achieved by a standard aqueous workup (hexane) then by flash column chromatography (silica gel, hexane eluent) to give the product (0.70 g, 54%) as a yellow oil.

¹H NMR (CDCl₃) δ 1.6(bs, 6H, 3CH₂), 2.0(s, 3H, CH₃), 2.4(m, 4H, allylic CH₂).

¹³C NMR (CDCl₃) δ 4.5(CH₃), 26.0, 27.0, 27.3, 33.5, 33.8, 77.3, 90.1, 94.3, 148.6. IR (neat) ν_{max} cm⁻¹: 2900, 2830, 2200 (acetylene), 1430. MS (EI), m/e (relative intensity) 214, 212 (M⁺, 70, 67). Glc R_t = 16.04 min.

In the cuprous bromide procedure, the crude cumulene **3** [R = CH₃, R', R" = (CH₂)₅] generated and isolated as above was stirred at 20° with CuBr (4.29 g, 30 mmol) in 30 ml CH₃CN under an argon atmosphere for 3 hrs. The reaction was filtered and the solvent replaced with hexane. Isolation and purification as stated above gave a 0.68 gm cyclohexane (1-bromo-2-butynylidene) (52%).

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References

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- (3) Ziegler, C. B., Jr.; Harris, S. M.; Baldwin, J. E. J. Org. Chem. 1987, **52**, 443.
- (4) Recently, a palladium-catalyzed substitution of 1,1-dichloroalkenes with acetylenes to yield 2-chloro-1-en-3-yne has been reported: Ratovelomanana, V.; Hammond, A.; Linstrumelle, G. Tetrahedron Lett. 1987, **27**, 1649. Also see Tellier, F.; Sauvetre, R.; Normant, J. F. Tetrahedron Lett. 1986, **27**, 3147.
- (5) Bromo[3]cumulenes originating from ketones generally are more stable than those derived from aldehydes. As described in Reference 3, ¹H, ¹³C NMR, IR and MS spectral characterization of one of the cumulene intermediates was reported. In this study such a spectral analysis was carried out on cyclohexane, (3-bromo-1,2-propadienylidene), **3** [R=H, R', R" = (CH₂)₅]. ¹H NMR (CDCl₃), δ 1.65(bs, 6H, 3CH₂), 2.3(m, 4H, allylic CH₂), 5.9(s², 1H, vinyl H). ¹³C NMR (CDCl₃) δ 25.7, 27.3 (2C), 34.5, 34.9, 75.85, 126.4, 150.0 (sp C), 158.9 (sp C). IR (neat) νmax cm⁻¹ 3050, 2920, 2870, 2840, 2820, 2050 (cumulene) 1650, 1440, 1430.
- (6) Bromo[3]cumulenes **3**, where R=H, were very slow to react with either CuI or CuBr. Presumably, decomposition pathways involving **3** competed with the S_N2' reaction. In instances involving **3**, where R=Ph, the phenyl substituted acetylenic product **4** is more likely to undergo a CuX/CuX₂ mediated halide substitution reaction (relative to cases where R=H or CH₃). See for example Schmid, G., in Chemistry of the Carbon-Carbon Triple Bond, Patai, S., ed.; Wiley: New York, 1978, pp. 320-322.
- (7) Some examples are the following: Corey, E. J.; Pyne, S. G. Tetrahedron Lett. 1983, **23**, 3291. Corey, E. J.; Kang, J. Tetrahedron Lett. 1982, **23**, 1651. Corey, E. J.; Kang, J. J. Am. Chem. Soc., 1981, **103**, 4618. Meijer, J.; Vermeer, P. Rec. Trav. Chim., 1974, **92**, 183.
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