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β-HALOVINYL KETONES: SYNTHESIS FROM ACETYLENIC KETONES

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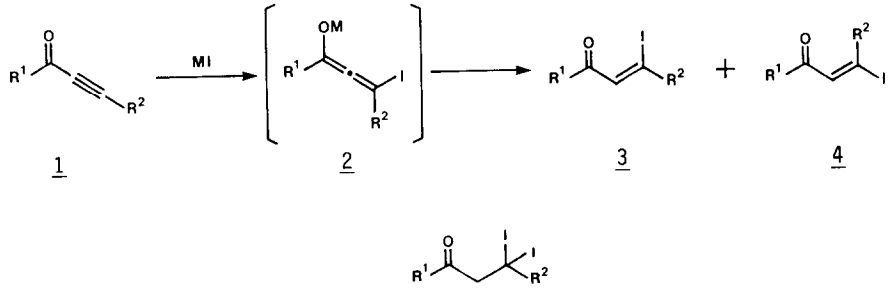
Abstract: The reaction of terminal acetylenic ketones with NaI or LiBr gave almost exclusively E-β-iodo- or E-β-bromovinyl ketones in trifluoroacetic acid, while Z-β-iodo- or Z-β-bromovinyl ketones were the major products in acetic acid. Trimethylsilyl iodide and bromide reacted smoothly with acetylenic ketones at -78°C to give TMS-allenolates which were readily converted to β-iodo- and β-bromovinyl ketones, respectively.

β-Halovinyl ketones have proved to be versatile and valuable materials in organic synthesis.[1] However, the synthesis of β-halovinyl ketones, especially β-iodovinyl ketones, often poses a difficult synthetic problem.[2] β-Iodovinyl ketones should, we hoped, be obtained via a Michael addition of iodide anion or its equivalent to acetylenic ketones in the presence of the reagent activating the carbonyl group, and it was found that trimethylsilyl iodide gave satisfactory results.[3] We have further studied the Michael reaction of iodide and bromide anions, or their equivalents, with acetylenic ketones in acidic media.

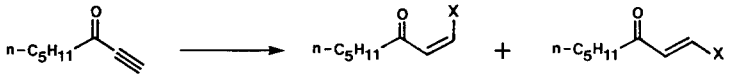
Scheme 1



1 2 3 4

5

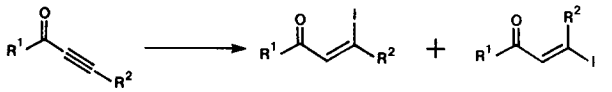
Table 1



1a 3a 4a

Reagents/Solvents	Conditions	3a (%)	4a (%)	x
NaI/TFA	RT, 30 min	--	95	I
NaI/AcOH	RT, 30 min	70	17	I
NaI/AcOH	RT, 21 hr	--	94	I
$n\text{-}Bu_4NI$/TFA (2 eq)/CH_2Cl_2	0°C, 2 hr	--	84	I
TMSI/CH_2Cl_2	-78°C, 10 min	--	91	I
LiBr/TFA	RT, 30 min	1	89	Br
LiBr/AcOH	RT, overnight	68	12	Br
TMSBr/CH_2Cl_2	-78°C, 10 min	22	64	Br
TMSCl/$CHCl_3$	reflux, 6 hr	16	6	Cl

Table 2



1 3 4

	Substrates R^1	R^2	Method[a]	Conditions	3 (%)	4 (%)
1b:	i-Pr	H	A	RT, 30 min	--	85
			B	RT, 30 min	65	9
1c:	Ph	H	A	RT, 30 min	--	78
			B	RT, 2 hr	66	23
1d:	n-Pen	Me	A	RT, 2 hr	28	59
			B	RT, 80 hr	21	17
1e:	n-Pen	n-Bu	A	RT, 30 min	27	67
			B	RT, 24 hr	11	16
1f:	n-Pen	Ph	A	RT, 1.5 hr	73	19
			B	RT, 40 hr	26	--
1g:	OMe	n-Bu	A,C	RT, 6 hr	<20	
1h:	$AcO(CH_2)_4$	n-Bu	C	-78°C, 5 min	33	56
1i:	$(t\text{-}Bu)(Me)_2SiO(CH_2)_4$	n-Bu	C	-78°C, 5 min	33	52
1j:	$THPO(CH_2)_4$	n-Bu	C	-78°C, 5 min	42	31

[a]Method A: NaI/TFA B: NaI/AcOH C: TMSI/CH_2Cl_2

We first examined the reaction of 1-octyn-3-one (1a: R^1=n-C_5H_{11}, R^2=H) with various iodinating reagents (Table 1). The reaction of 1a with NaI (1 eq) in trifluoroacetic acid (TFA), $(n\text{-}Bu)_4NI$ (1 eq) in CH_2Cl_2 containing 2 equivalents of TFA, or trimethylsilyl iodide (TMSI) in methylene chloride gave exclusively the E-β-iodovinyl ketone 4a (R^1=n-C_5H_{11}, R^2=H; mp 38°C, lit. mp 36-37°C[2a]) in high yield.[4,5] The Z-isomer 3a (R^1=n-C_5H_{11}, R^2=H) was obtained as the major product with NaI in AcOH at room temperature for 30 min. It seems reasonable to interpret this stereochemical outcome in terms of the steric hindrance exerted by the iodine atom for protonation at the α-position. As anticipated, upon thermodynamic equilibration the E-isomer was found to be the sole product under the conditions of NaI/AcOH/21 hr. It was interesting to note that two equivalents of NaI in TFA yielded the diiodide 5a (R^1=n-C_5H_{11}, R^2=H), which was converted to 4a in good yield upon treatment with diisopropylethylamine in CH_2Cl_2 at room temperature. As reported in the preceding paper,[3] TMSI smoothly reacted with 1a at -78°C to yield the unstable but spectroscopically detectable TMS-allenolate 2a (R^1=n-C_5H_{11}, R^2=H, M=TMS), from which the E-iodovinyl ketone 4a was obtained in high yield.

The reactivity of 1a towards LiBr/TFA, LiBr/AcOH or trimethylsilyl bromide was found parallel to the iodo series. However, the current method is not highly effective for the preparation of β-chlorovinyl ketones; trimethylsilyl chloride reacted sluggishly with 1a even under reflux in $CHCl_3$.

We next applied these reaction conditions to a variety of substituted acetylenic ketones (Table 2). Terminal acetylenic ketones such as 1b,c gave results similar to 1a; the E-isomer was formed as the sole product in TFA containing NaI, whereas the Z-isomer was the major product in AcOH containing NaI. As might be expected, the behavior of inner acetylenic ketones was different from that of terminal acetylenic ketones. The conditions of NaI/TFA and of TMSI/CH_2Cl_2 were as effective for inner cases as for terminal cases, but the conditions of NaI/AcOH were less effective for inner cases. The E versus Z selectivity for inner cases was lower than for terminal cases, which shows the fine balance of thermodynamical stability of the E- and Z-isomers, dependent on the electronic as well as steric effects of the substituents. We have also tested these conditions for acetylenic ester 1g with limited success.[6]

In general, E- and Z-isomers show a large difference in mobility on silica gel, and they are easily separable by conventional silica gel column chromatography. In addition, since base treatments of E- and Z-β-iodovinyl ketones regenerate acetylenic ketones, either isomer can be recycled.[3]

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References and Footnotes

1. β-Chlorovinyl ketones have been used for the preparations of β-substituted vinyl ketones and heterocyclic compounds such as isoxazoles and pyrazoles: for example, see A. E. Pohland and W. R. Benson, Chem. Rev., 66, 161 (1966). β-Iodo- or β-bromovinyl ketones are the useful synthetic precursors for the corresponding vinyl halides, which provide easy access to organometallic reagents and subsequent carbon-carbon bond formations, well-known in the prostaglandin area: for example, see (a) A. Mitra, "The Synthesis of Prostaglandins," Wiley Interscience, 1977, New York. (b) J. S. Bindra and R. Bindra, "Prostaglandin Synthesis," Academic Press, 1977, New York.

2. β-Chlorovinyl ketones are readily prepared from acyl chlorides and acetylenes in the presence of a Lewis acid. Only a few methods were reported for the syntheses of β-iodovinyl ketones. These include: 1. a route via β-chlorovinyl ketones [E. J. Corey and B. J. Beames, J. Am. Chem. Soc., 94, 7210 (1972)], 2. a route via β-diketones [E. Piers, J. R. Grierson, C. K. Lau, and I. Nagakura, Can. J. Chem., 60, 210 (1982)], and 3. a route via 1-iodo-2-trimethylsilyl ethylene [J.-P. Pillot, J. Dunogues, and R. Calas, Synth. Commun., 9, 395 (1979)].

3. S. H. Cheon, W. J. Christ, L. D. Hawkins, H. Jin, Y. Kishi, and M. Taniguchi, Tetrahedron Lett., 27, 0000 (1986).

4. Satisfactory spectroscopic data were obtained for all the compounds reported in this paper.

5. The stereochemistry of E- and Z-halovinyl ketones was assigned as follows: 1. 3a-c and 4a-c were based on the chemical shifts and spin-spin coupling constants of the vinyl protons in the ^{1}H-NMR spectra, 2. 3d,e and 4d,e were based on the deshielding effect of the carbonyl group shifting the signal due to the γ-methyl or γ-methylene protons of the E-isomer to the lower field than the corresponding Z-isomer, and 3. 3e,f and 4e,f were based on the reductive removal of the iodine (Zn/MeOH), followed by NMR analyses.

6. Michael addition of HI to propiolic acid is known; see K. Bowden and M. J. Price, J. Chem. Soc. (B), 1466 (1970) and references cited therein. Also see M. E. Jung, J. A. Hagenah, and L.-M. Zeng, Tetrahedron Lett., 24, 3973 (1983).

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