Efficient Synthesis of 4-Halo-4-penten-2-ones and 3-Halo-3-butenoic Acids/Esters via Hydrohalogenation Reaction of 3,4-Pentadien-2-one and 2,3-Butadienoic Acid/Methyl Ester

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Recently, much attention has been paid to the chemistry of allenes, due to their high and unique reactivity.[1,2] Both electrophilic and nucleophilic addition of allenes have been observed.[1] Usually, one of the two C−C double bonds present in allenes can be selectively reacted to provide vinylic products via delicate tuning of the steric and electronic factors. During the course of our studies toward the synthesis of butenolide-containing natural products, we were interested in the methodology for the efficient synthesis of 3-halo-3-butenols, which can be prepared from 2-halo-2-propenyl ketones.

In principle, β,γ-unsaturated enones could be prepared by the formation of either the C−C double bond or the C−O double bond; however, the potential migration of the C=C bond from the β,γ-position to the α,β-position is a problem.[3,4] Hydrochlorination of allenic ketones by HCl did not yield useful results; the main reaction that occurred was polymerization, while hydrochlorination using *N,N′*-dimethylhydrazine dihydrochloride afforded a mixture of β,γ- and α,β-enones with Cl at the β-position.[4]

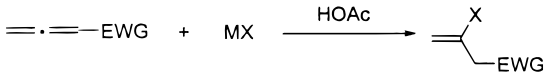
After several attempts, we found that the title compounds can be easily synthesized from the reactions of the readily available 3,4-pentadien-2-one with lithium halides in acetic acid at 25 °C. The results are summarized in Scheme 1. LiI, LiBr, and LiCl all afforded the corresponding 4-halo-4-penten-2-ones in good yields.

The results in Scheme 1 stimulated our interest in the corresponding reaction of 2,3-butadienoic acid and its esters. The results are summarized in Table 1. The following points should be noted for this reaction:

(1) 3,4-Pentadien-2-one is more reactive than 2,3-butadienoic acid and its ester: for the acid/ester, the reaction is slow at 25 °C and usually was carried out at 70 °C.

(2) Sodium halides are also effective for this transformation (Table 1, entries 4, 6, and 8), albeit slower compared to lithium halides (compare Scheme 1 with entries 1−3 in Table 1). In the presence of both NaI and NaCl (1:1), 3,4-pentadien-2-one afforded **2a** and **2c** in a ratio of 2:1 (eq 1).

Table 1. Synthesis of 2-Halo-2-propenyl Ketones and 3-Halo-3-butenoic Acids/Esters

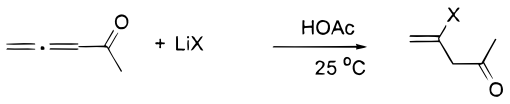


1 **2**

entry	EWG	MX	temp/time (°C/h)	product **2**	yield[a] (%)
1	$COCH_3$	NaI	25/1.5	**2a**	69
2	$COCH_3$	NaBr	25/14	**2b**	35[b]
3	$COCH_3$	NaCl	25/25	**2c**	8[b]
4	COOH	NaI	70/7	**2d**	92
5	COOH	HI[c]	70/7	**2d**	87
6	COOH	NaBr	70/7	**2e**	82[b]
7	COOH	$LiBr·H_2O$	70/7	**2e**	88
8	COOH	NaCl	70/15	**2f**	16[b]
9	COOH	$LiCl·H_2O$	70/7	**2f**	87
10	CO_2CH_3	NaI	70/0.5	**2g**	56
11	CO_2CH_3	$LiBr·H_2O$	70/18	**2h**	86
12	CO_2CH_3	$LiCl·H_2O$	70/26	**2i**	74

[a] Isolated yield, only otherwise stated. [b] The yield was determined by ^1H NMR using CH_2Br_2 as the internal standard. [c] Aqueous hydriodic acid (45%) was used.

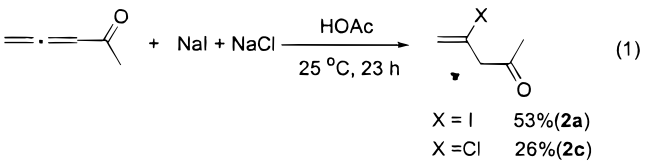
Scheme 1



1a

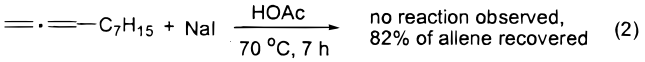
LiX	time (h)	Isolated yield (%)
X = I	4	**2a** 82
Br[a]	13	**2b** 80
Cl[a]	22	**2c** 80

[a] The monohydrate of LiX was used.



(1)

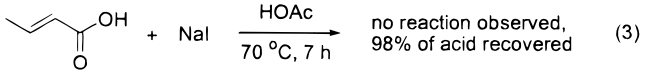
(3) Allenes without an electron-withdrawing group, e.g., 1,2-decadiene, do not react with NaI in HOAc under similar conditions (eq 2). All these imply that the



(2)

reaction proceeds via nucleophilic addition of halides to the α,β C=C bond of allenes **1**. Although the central carbon atom of an ordinary alkyl-substituted allene is electrophilic in nature (see p 56 of ref 1), it is not electrophilic enough to trigger this nucleophilic addition.

(4) No reaction was observed in the treatment of crotonic acid with NaI in HOAc at 70 °C for 7 h (eq 3). Thus, it is obvious that both the high reactivity of the cumulated C=C bonds and the electron-withdrawing group account for this interesting nucleophilic addition reaction.



(3)

(1) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; John Wiley & Sons: New York, 1988.
(2) *The Chemistry of Ketenes, Allenes, and Related Compounds*; Patai, S., Ed.; John Wiley & Sons: New York, 1980; Part 1.
(3) Tidwell, T. T. *Org. React.* **1990**, *39*, 297 and references cited therein.
(4) Gras, J.-L.; Galledou, B. S. *Bull. Soc. Chim. Fr.* **1983**, II-89.

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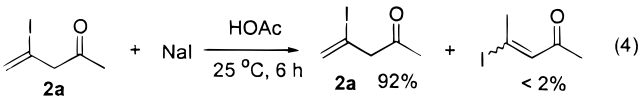
(5) Although 3−4% of 4-iodo-3-penten-2-one was formed by the reaction of NaI and **1a** in HOAc for 1.5 h, under the present conditions, the migration of the C=C double bond of **2** from the β,γ-position to the α,β-position was not serious:[4] the reaction of **2a** with NaI at 25 °C in HOAc afforded 4-iodo-3-penten-2-one in <2% yield, while **2a** was recovered in 92% yield (eq 4).



(4)

Previously, 3-halo-3-butenoic acids and esters were prepared by Pd-catalyzed carboxylation reactions of propargyl halides,[5] hydrolysis of the corresponding nitriles, which, in turn, were prepared in several steps,[6] and addition of HX to 2,3-butadienoic acid[7] (X = I, entry 5, Table 1) and its ester,[8] the present method provides a simple, mild, and efficient route to β-halo-β,γ-unsaturated butenoic acids, esters, and 4-halo-4-penten-2-ones. These compounds are important intermediates in organic synthesis because of the four reaction sites presented, i.e., the carbonyl group, the C=C bond, the C−X bond, and the activated α-methylene group; this novel methodology will show its utility in organic synthesis. The scope of this reaction and its synthetic application are being investigated in our laboratory.

Experimental Section

Starting Materials. 3,4-Pentadien-2-one,[9] 2,3-butadienoic acid,[6] 1,2-decadiene,[10] and 2,3-butadienoic acid methyl ester[11] were prepared according to the published procedures. LiI, lithium bromide monohydrate, lithium chloride monohydrate, NaI, NaBr, NaCl, and crotonic acid were commercially available and used without purification. The ^{1}H NMR spectra were recorded using $CDCl_3$ as the solvent.

Synthesis of 4-Iodo-4-penten-2-one (2a). Typical Procedure. A solution of 3,4-pentadien-2-one (164 mg, 2.0 mmol) and NaI (330 mg, 2.2 mmol) in HOAc (1 mL) was stirred at rt for 1.5 h. After complete conversion of the starting material, the mixture was diluted with ether and neutralized with aqueous K_2CO_3 at 0 °C. The ether layer was separated, the aqueous layer was extracted with ether, and the combined ether layers were dried over $MgSO_4$. Evaporation of the solvent and chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) afforded 4-iodo-4-penten-2-one (**2a**) in 69% yield (290 mg). **4-Iodo-4-penten-2-one (2a)**: liquid; ^{1}H NMR δ 2.21 (s, 3H), 3.64 (s, 2H), 5.95 (s, 1H), 6.18 (s, 1H); MS (*m*/*e*) 210 (M^+, 14.35), 43 (100); IR (neat) 1714, 1614 cm^{-1}; HRMS calcd for C_5H_7IO 209.9542, found 209.9531.

The following compounds were prepared similarly using the conditions listed in Scheme 1 and Table 1.

4-Bromo-4-penten-2-one (2b): liquid; ^{1}H NMR δ 2.22 (s, 3H), 3.54 (s, 2H), 5.64 (s, 1H), 5.74 (s, 1H); MS (*m*/*e*) 164 (M^+(^{81}Br), 10.40), 162 (M^+(^{79}Br), 10.39), 43 (100); IR (neat) 1718, 1626 cm^{-1}; HRMS calcd for C_5H_7BrO(^{79}Br) 161.9680, found 161.9714.

4-Chloro-4-penten-2-one (2c): liquid; ^{1}H NMR δ 2.23 (s, 3H), 3.42 (s, 2H), 5.31 (s, 1H), 5.41 (s, 1H); MS (*m*/*e*) 120 (M^+(^{37}Cl), 2.78), 118 (M^+(^{35}Cl), 9.75), 43 (100); IR (neat) 1716, 1628 cm^{-1}; HRMS calcd for C_5H_7ClO(^{35}Cl) 118.0185, found 118.0186.

3-Iodo-3-butenoic acid (2d):[7a] mp 64−65 °C; ^{1}H NMR δ 3.63 (s, 2H), 5.96 (s, 1H), 6.24 (s, 1H), 8.00 (bs, 1H); MS (*m*/*e*) 212 (M^+, 100); IR (neat) 3094, 1697, 1619 cm^{-1}.

3-Bromo-3-butenoic acid (2e):[7b,c] mp 48−50 °C (lit.[7c] mp 46−47 °C); ^{1}H NMR δ 3.56 (s, 2H), 5.68 (s, 1H), 5.82 (s, 1H), 8.75 (bs, 1H); MS (*m*/*e*) 166 (M^+(^{81}Br), 11.38), 164 (M^+(^{79}Br), 11.27), 44 (100); IR (neat) 3054, 1697, 1597 cm^{-1}.

3-Chloro-3-butenoic acid (2f):[6] mp 32−34 °C (lit.[6b] mp 31−32 °C); ^{1}H NMR δ 3.38 (s, 2H), 5.37 (s, 1H), 5.42 (s, 1H), 7.25 (bs, 1H); MS (*m*/*e*) 122 (M^+(^{37}Cl), 9.92), 120 (M^+(^{35}Cl), 3.05), 103 (100); IR (neat) 3056, 1701, 1597 cm^{-1}.

3-Iodo-3-butenoic acid methyl ester (2g): liquid; ^{1}H NMR δ 3.51 (s, 2H), 3.68 (s, 3H), 5.85 (s, 1H), 6.14 (s, 1H); MS (*m*/*e*) 226 (M^+, 8.08), 73 (100); IR (neat) 1740, 1618 cm^{-1}; HRMS calcd for $C_5H_7IO_2$ 225.9491, found 225.9492.

3-Bromo-3-butenoic acid methyl ester (2h): liquid; ^{1}H NMR δ 3.51 (s, 2H), 3.73 (s, 3H), 5.64 (s, 1H), 5.79 (s, 1H); MS (*m*/*e*) 180 (M^+(^{81}Br), 13.73), 178 (M^+(^{79}Br), 12.48), 99 (100); IR (neat) 1742, 1632 cm^{-1}; HRMS calcd for $C_5H_7BrO_2$(^{79}Br) 177.9629, found 177.9626.

3-Chloro-3-butenoic acid methyl ester (2i):[12] liquid; ^{1}H NMR δ 3.21 (s, 2H), 3.68 (s, 3H), 5.28 (s, 1H), 5.32 (s, 1H); MS (*m*/*e*) 136 (M^+(^{37}Cl), 4.02), 134 (M^+(^{35}Cl), 11.55), 43 (100); IR (neat) 1742, 1634 cm^{-1}.

The reactions shown in eqs 1−4 were carried out as above, and the yields were determined by ^{1}H NMR using CH_2Br_2 as the internal standard.

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Supporting Information Available: ^{1}H NMR spectra of compounds **2a**−**c** and **2g**−**h** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(5) Nogi, T.; Tsuji, J. *Tetrahedron* **1969**, *25*, 4099.
(6) (a) Théron, F.; Vessière, R. *Bull. Soc. Chim. Fr.* **1968**, 2254. (b) Vessière, R. *Compt. Rend.* **1956**, *243*, 593.
(7) (a) Duchêne, A.; Aborbri, M.; Parrain, J. L.; Kitomura, M.; Noyori, R. *Synlett.* **1994**, 524. (b) Rosenquist, N. R.; Chapman, O. L. *J. Org. Chem.***1976**, *41*, 3326. (c) Vessière, R.; Théron, F. *C. R. Acad. Sci.* **1961**, *253*, 676.
(8) (a) Rosenthal, R. W.; Schwartzman, L. H. *J. Org. Chem.* **1959**, *24*, 836. (b) Kurtz, P.; Gold, H.; Disselnkötter, H. *Ann.* **1959**, *624*, 1.
(9) Buono, G. *Synthesis* **1981**, 872.
(10) Venkruijsse, H. D.; Brandsma, L. *Synthesis of Acetylenes, Allenes and Cumulenes. A Laboratory Manual*; Elsevier: Amsterdam, 1981; p 156.
(11) Lang, R. W.; Hansen, H. J. *Helv. Chim. Acta* **1980**, *63*, 438.
(12) Susuki, T.; Tsuji, J. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1954.