1,1-Bifunctional Cyclopropanes; Convenient Synthesis of 1-Bromo-, 1-Chloro-, and 1-Fluorocyclopropyl Methyl Ketone

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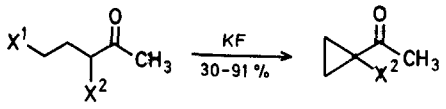
Base-promoted cyclization of 5-halo-2-pentanones via enolates is an important route to cyclopropyl methyl ketones[1].

As the halogenation of ketones facilitates their enolization, it seemed attractive to start with 3,5-dihalo-2-pentanones (**1**) in searching for a simple access to the so far unknown *1-halocyclopropyl methyl ketones* (**2**). These compounds would be of considerable synthetic value, as they would allow reactions of choice at both functions present[2].

We report here that 1-bromo-, 1-chloro-, and 1-fluorocyclopropyl methyl ketones (**2a–c**) may be obtained by simply heating the appropriate 3,5-dihalo-2-pentanone (**1**) with potassium fluoride as base[3].



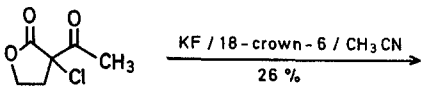
1

1	X^1	X^2
a	Br	Br
b	Br	Cl
c	Br	F
d	Cl	Br
e	Cl	Cl
f	Cl	F

2

2	X^2
a	Br
b	Cl
c	F

Starting compounds **1a**[4,5], **1b**[6], **1d**[5,7], and **1e**[8] were prepared according to literature reports. 5-Bromo-3-fluoro-2-pentanone (**1c**) was synthesized by chlorine/fluorine exchange in 2-acetyl-2-chloro-4-butanolide (**3**)[9] with subsequent ring opening and decarboxylation of the resultant fluoro derivative **4** by means of hydrobromic acid. 5-Chloro-3-fluoro-2-pentanone (**1f**) was obtained more simply by bromine/fluorine exchange in **1d**.



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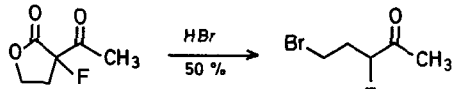

4 **1c**

As examined in the case of **1a**, various base/solvent systems (sodium hydroxide/ether, sodium amide/ether, potassium *t*-butoxide/ether, potassium *t*-butoxide/*t*-butyl alcohol, and potassium fluoride/diethylene glycol) effected cyclization to **2a**. The best results were obtained with potassium fluoride/diethylene glycol as base/solvent system. When **1a** was added to this system maintained at 110°/20 torr, nearly pure 1-bromocyclopropyl methyl ketone (**2a**) distilled off. This prompted us to look more closely at the scope and limitation of this cyclization and to react other 3,5-dihalo-2-pentanones with potassium fluoride as well.

As can be seen from Table 1, all 3,5-dihalo-2-pentanones **1**, except **1d** and **1f**, cyclize to the corresponding 1-halocyclopropyl methyl ketones **2** on simply heating the reactants in diethylene glycol at 110°[10]. At this temperature **1d** suffers bromine/fluorine exchange to give **1f**, which in turn cyclizes to give **2c** on raising the temperature up to 160°.

Comparing the different possibilities indicated in Table 1, we recommend examples 1, 3, and 6 as being the most convenient for the synthesis of the 1-halocyclopropyl methyl ketones **2a**, **2b**, and **2c**, respectively.

Reagents. Potassium fluoride (Merck) was dried at 180°/5 torr for 12 h prior to use. Acetonitrile was refluxed over phosphorus pentoxide and distilled. Diethylene glycol was commercial grade (Merck) and used without further purification.

Preparation of 2-Acetyl-2-fluoro-4-butanolide (4):
2-Acetyl-2-chloro-4-butanolide[9] (**3**; 162.5 g, 1.0 mol), potassium fluoride (174.3 g, 3.0 mol), 18-crown-6 (0.1 g), and acetonitrile (700 ml) are heated under reflux for 104 h. Most of the solvent is then distilled off at atmospheric pressure. The remaining material is distilled to dryness in vacuo and the distillate redistilled through a 80-cm Vigreaux column to give **4**; yield: 37.4 g (26%); b.p. 99–103°/11 torr. For analytical and spectral data see Table 2.

Preparation of 5-Bromo-3-fluoro-2-pentanone (1c):
Compound **4** (73.0 g) and 48% hydrobromic acid (280 ml) are stirred at 60° for 3 h. The reaction mixture is poured into water (400 ml), and extracted twice with 200 ml-portions of ether. The combined ether solutions are washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride solutions, dried over molecular sieves, and evaporated to a yellow liquid (82.4 g) which is distilled to give **1c**; yield: 45.6 g (50%); b.p. 71–73°/14 torr. For analytical and spectral data see Table 2.

Preparation of 1-Halocyclopropyl Methyl Ketones (2a-c) and 5-Chloro-3-fluoro-2-pentanone (1f); General Procedure:
A suitable two-necked flask equipped with a magnetic stirrer bar, pressure equalizing addition funnel, and short path distillation apparatus is charged with potassium fluoride (0.2–1.5 mol, see Table 1) in diethylene glycol (40–300 ml, see Table 1). Under reaction conditions indicated in Table 1, the appropriate 3,5-dihalo-2-pentanone **1** (0.1–0.5 mol, see Table 1) is added with stirring at such a rate as to maintain distillation of products being formed (30 min). After addition is complete, the pressure is reduced within 15 min to 10 torr (for examples 5 and 6, 60 torr) in order to remove last traces of products. The distillate

Table 1. Preparation of 1-Halocyclopropyl Methyl Ketones (**2a-c**) and 5-Chloro-3-fluoro-2-pentanone (**1f**)

Starting Compound **1**	**1** (mol)/KF (mol)/ solvent (ml)	Reaction Conditions	Product	Yield [%]	b.p./torr
1a	0.5/1.0/200	110°/20 torr	**2a**	62	85°/120
1b	0.2/0.4/80	110°/60 torr	**2b**	91	69°/120
1e	0.5/1.0/200	110°/60 torr	**2b**	68	
1c	0.1/0.2/40	110°/70 torr	**2c**	40	88°/760
1f	0.1/0.2/40	160°/180 torr	**2c**	30	
1d	0.5/1.5/300	160°/180 torr	**2c**	12	
1d	0.5/1.0/200	110°/15 torr	**1f**	28	56°/13

Table 2. Analytical Data for 3,5-Dihalo-2-pentanones (**1c** and **1f**), 1-Halocyclopropyl Methyl Ketones (**2a-c**), and 2-Acetyl-2-fluoro-4-butanolide (**4**)

Compound	Molecular formula[a]	I.R. (neat) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]	^{19}F-N.M.R. ($CFCl_3$) δ [ppm]
1c	C_5H_8BrFO (183.0)	1722	1.85–2.65 (m, 2H), 2.27 (d, 3H, $^4J_{HF}$ = 5 Hz), 3.46 (dd, 2H, $^3J_{HH}$ = 5.5 and 6.0 Hz), 4.77 (m, 1H, $^2J_{HF}$ = 48 Hz)	193.0 (m, $^4J_{HF}$ = 5 Hz, $^2J_{HF}$ = 48 Hz)
1f	C_5H_8ClFO (138.6)	1728	1.85–2.65 (m, 2H), 2.27 (d, 3H, $^4J_{HF}$ = 5 Hz), 3.65 (dd, 2H, $^3J_{HH}$ = 5.5 and 6.0 Hz), 4.87 (m, 1H, $^2J_{HF}$ = 48 Hz)	193.2 (m, $^4J_{HF}$ = 5 Hz, $^2J_{HF}$ = 48 Hz)
2a	C_5H_7BrO (163.0)	1702	1.43 (AA'BB', 4H), 2.47 (s, 3H)	
2b	C_5H_7ClO (118.6)	1704	1.42 (AA'BB', 4H), 2.46 (s, 3H)	
2c	C_5H_7FO (102.1)	1712	1.05–1.45 (m, 4H), 2.37 (d, 3H, $^4J_{HF}$ = 5Hz	196.4 (m, $^4J_{HF}$ = 5 Hz)
4	$C_6H_7FO_3$ (146.1)	1724, 1789	2.10–3.10 (m, 2H), 2.43 (d, 3H, $^4J_{HF}$ = 5 Hz), 4.20–4.55 (m, 2H)	163.1 (m, $^4J_{HF}$ = 5 Hz)

[a] All compounds gave satisfactory microanalyses (C ±0.2%, H ±0.1%, Halogen ±0.24%).

is then dried over magnesium sulphate and fractionated through a Spaltrohr-Column to give the desired ketones **2a, 2b, 2c,** and **1f** in yields indicated in Table 1. For analytical and spectral data see Table 2.

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[1] J. M. Conia, *Angew. Chem.* **80,** 578 (1968); *Angew. Chem. Int. Ed. Engl.* **7,** 570 (1968).

[2] For the synthesis and application of the closely related 1,1′-dibromodicyclopropyl ketone see L. Fitjer, *Angew. Chem.* **88,** 803, 804 (1976); *Angew. Chem. Int. Ed. Engl.* **15,** 762, 763 (1976).

[3] Potassium fluoride has been reported to effect cyclization of 4-chloro- and 4-bromobutyryl fluoride to cyclopropane carboxylic acid fluoride (R. E. A. Dear, E. E. Gilbert, *J. Org. Chem.* **33,** 1960 (1968)).

[4] H. Andersag, K. Westphal, *German Patent (DRP)* 704236 (1941), I.G. Farben; *C.A.* **36,** 1046 (1942).

[5] If **1a** (b.p. 50°/0.001 torr) and **1d** (b.p. 32–34°/0.001 torr) are distilled at temperatures higher than those given above, disproportionation to mono- and trihalo-2-pentanones may occur.

[6] U. Schmidt, P. Grafen, H. W. Goedde, *Justus Liebigs Ann. Chem.* **670,** 157 (1963).

[7] N. W. Kuznetsov, R. A. Myrsina, *Ukr. Khim. Zh.* **41,** 1186 (1975); *C.A.* **84,** 105311 (1976).

[8] R. König, A. Gerecs, Z. Földi, *Acta Chim. Acad. Sci. Hung.* **3,** 157 (1953).

[9] R. Buchman, *J. Am. Chem. Soc.* **58,** 1803 (1936).

[10] Attempted cyclization of **1d** and **1e** with sodium methoxide/methanol as base/solvent system has been reported [7] to yield 3,4,4-trimethoxy-1-pentanol.