Synthesis of γ-Chloro (β-Chloromethyl) Ketones from α-Cyclopropyl Ketones

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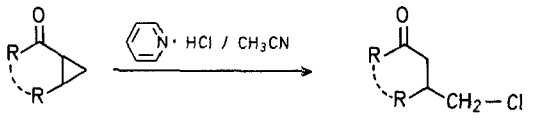
We recently reported that pyridine hydrochloride in pyridine was a mild reagent for nucleophilic cleavage of a conjugate and fused cyclopropyl ring[1].

The more polar solvent acetonitrile allowed us to apply this reaction to other α-cyclopropyl ketones and to provide a convenient method for the synthesis of γ-chloro ketones, potential intermediates for azabicycloalkanes[1]. A range of alicyclic ketones were treated with 2 equiv of pyridine hydrochloride in acetonitrile. In four substrates the cyclopropane ring was conjugated with the carbonyl function and condensed with another ring. Furthermore, cyclopropyl methyl ketone reacted as well. The results are summarized in the Table. Ring opening always afforded γ-chloro ketones in yields ranging from 70 to 82%, after reaction times of 11–42 h.



1 2

The characterization of the reaction products was based on their spectral data (see Table) and by comparison with an authentic sample (in the case of 4-chlorocyclohexanone[2]) or with the literature spectral data (for 5-chloropentan-2-one[3]). 1-Acetyl-2-chloromethylcyclohexane was a single product on several G.L.C. columns; in the N.M.R. spectrum the $-CH_2Cl$ group was a clean AB part of an ABX system. The *trans* stereochemistry rests on several equilibration trials giving only the starting material and on the analogy with other nucleophilic cyclopropane ring opening[4] reactions.

I.R. spectra were recorded on a Perkin-Elmer 257 Infracord instrument. ^{1}H-N.M.R. spectra were obtained on a Perkin-Elmer R 32 90-MHz spectrometer, using TMS as an internal standard. Mass spectra were performed with an AEI-MS 12 spectrometer at an ionization potential of 70 eV. G.L.C. analyses were carried out with a Perkin-Elmer F 11, using 2 m, 1/8″ columns, packed with OV 17 (2%) and LAC 886 (4%) on Chromosorb W.

Cyclopropyl methyl ketone was a commercial product (EGA). Bicyclo[3.1.0]hexan-2-one[5], bicyclo[5.1.0]octan-2-one[6], 1-acetylbicyclo[4.1.0]heptane[7] were prepared by the Corey method starting, respectively, from cyclopenten-2-one (EGA), cyclohepten-2-one[8], and 1-acetylcyclohexene (EGA). Pyridine hydrochloride was prepared according to a reported procedure[9].

Preparation of γ-Chloro Ketones; General Procedure:
α-Cyclopropyl ketone (10 mmol) and pyridine hydrochloride (20 mmol) are refluxed in acetonitrile (25 ml, distilled from calcium hydride) during a time of 11–42 h. The reaction mixture is poured into a saturated sodium chloride solution (25 ml) and extracted several times with ether. After washing of the ethereal layers with saturated sodium chloride solution and drying on anhydrous sodium sulfate, the solvent is removed and the residue chromatographed on silica gel. Elution with benzene/ethyl acetate (9:1) first afforded the γ-chloro ketones and then the starting materials. The yields reported in the Table were calculated on these quantities and the purity of products was tested by G.L.C.

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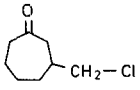
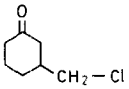
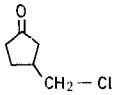
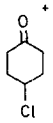
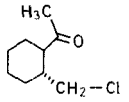
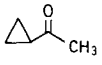
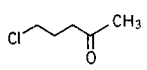
Table. γ-Chloro Ketones **2** from α-Cyclopropyl Ketones **1**

Substrate **1**	Product **2**	Reaction time	Yield [%]	b.p./torr (Lit. b.p./torr)	Molecular formula[a]	I.R.(CCl_4) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]	Mass spectra *m/e* (relative intensity)
		42 h	76	111–113°/20	$C_8H_{13}ClO$ (160.6)	1703	3.45 (m, 2H, CH_2Cl)[b]	162 (4, M+2); 160 (14); 132 (29); 125 (12); 124 (21); 116 (39); 111 (19); 97 (28); 81 (32); 67 (33); 55 (100)
		11 h	76	101–104°/20	$C_7H_{11}ClO$ (146.6)	1720	3.45 (m, 2H, CH_2Cl)	148 (10, M+2); 146 (31); 111 (6); 110 (6); 103 (31); 97 (94); 82 (31); 68 (28); 55 (100)
		28 h	39	79–81°/20	C_6H_9ClO (132.6)	1755	3.55 (m, 2H, CH_2Cl)	134 (13, M+2); 132 (38); 103 (23); 97 (14); 83 (100); 55 (82)
			36	96–98°/20 (95°/17)	C_6H_9ClO (132.6)	1725	4.40 (m, 1H, >CHCl)	134 (5, M+2); 132 (16); 97 (11); 91 (11); 79 (36); 68 (30); 55 (100)
		23 h	70	116–119°/20	$C_9H_{15}ClO$ (174.6)	1710	3.25 (2d, 2H, CH_2Cl)[c]	176 (3, M+2); 174 (8); 139 (8); 138 (20); 95 (78); 81 (35); 67 (34); 43 (100)
		26 h	82	70–73°/20 (75–77°/23)	C_5H_9ClO (120.6)	1715	3.50 (t, 2H, CH_2Cl)	122 (3, M+2); 120 (9); 105 (6); 85 (4); 84 (7); 77 (5); 58 (43); 43 (100)

[a] All products gave satisfactory microanalyses (C ±0.26, H ±0.18, Cl ±0.29).
[b] In $CDCl_3$.
[c] In C_6D_6.

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