1-Halo-3-phenylpropan-2-ones from Diazoketones

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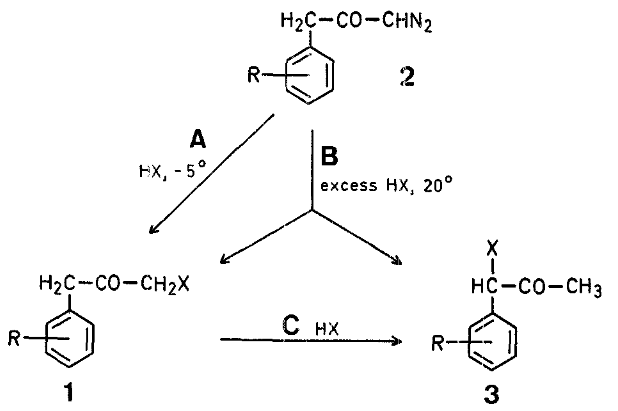
One of the classic synthetic routes to monohalomethyl ketones (**1**) is by reaction of the corresponding diazoketone (**2**) with the appropriate hydrogen halide or hydrohalic acid, such reactions normally being carried out with only moderate cooling and with excess of the acid[1]. During an attempt to apply this procedure to the synthesis of 1-chloro-2-oxo-3-(3,4-dimethoxyphenyl)-propane [**1**, $R = 3,4\text{-}(OCH_3)_2$, $X = Cl$], we obtained solely the isomeric 1-halo-1-phenyl ketone [**3**, $R = 3,4\text{-}(OCH_3)_2$, $X = Cl$] in good yield. Further investigation of a variety of substituted benzyl diazoketones revealed that the latter type of ketone was the sole product under the conditions normally employed if the benzyl substituents were electron donating mesomerically (Table 1). Moreover, such ketones were readily obtained from the 1-halo-3-phenylpropan-2-ones **1** by treatment of the latter with ethereal hydrogen bromide or hydrogen chloride, in marked contrast to those containing electron-withdrawing substituents which were comparatively stable under such conditions. Only one such isomerisation has been reported previously[2] and, although a dehalogenation – halogenation mechanism can be envisaged, the mechanism of the rearrangement remains uncertain. It is likely that isolation of the 1-halo-1-phenyl ketones **3** involves an isomerisation of the initially formed 1-halo-3-phenyl ketones **1**, and attempts to prepare 1-halo-3-phenylpropan-2-ones by this route should bear in mind the following information:

(a) Substitution in the phenyl ring by mesomerically electron-donating groups strongly promotes isomerisation, which is retarded in the presence of electron-withdrawing substituents. Compounds such as 1-bromo-3-(3,4-dimethoxyphenyl)-propan-2-one rapidly isomerised even on standing, while 1-bromo-3-(2,4-dinitrophenyl)-propan-2-one was unchanged after boiling with hydrogen bromide. Indeed, the latter has been prepared by hydrogen bromide-isomerisation of 1-bromo-1-(2,4-dinitrophenyl)-propan-2-one[3].

(b) Bromomethyl ketones are more liable to isomerise than chloromethyl ketones. 1-Bromo-3-phenylpropan-2-one readily isomerised on treatment with ethereal hydrogen bromide at 20° but the corresponding chloro-ketone was unchanged by similar treatment with ethereal hydrogen chloride.

(c) Isomerisation is favoured by the use of the normal conditions of room temperature and excess of hydrogen halide. Conversely, low temperatures ($< -5°$) and the use of the calculated amount of hydrogen halide retards isomerisation and permits isolation of the unstable 1-halo-3-phenylpropan-2-ones (**3**).



1-Halo-2-oxo-3-phenylpropanes (3) from Diazoketones (2); General Procedure:

An ethereal solution of the phenylacetyl chloride (0.1 mol) was added dropwise to an ethereal solution of diazomethane (0.1 mol) at 0°, and the solution was stirred for 5 hr before being stood overnight. Normally, decomposition was carried out by dropwise addition of the concentrated hydrohalic acid or by slow passage of gaseous hydrogen halide until the evolution of nitrogen ceased. The haloketone was then isolated by separation, washing the ethereal layer with water, drying (Na_2SO_4), and distillation. In cases where isomerisation was possible, the desired 1-halo-3-phenylpropan-2-ones were obtained by dropwise addition of ethereal hydrogen bromide or hydrogen chloride (0.1 mol), the temperature being kept below $-5°$, and the product obtained as before. Yields were generally of the order 60–70%, and ketones were purified by distillation or recrystallisation from benzene. Isomerisation of susceptible 1-halo-3-phenyl-propan-2-ones was retarded by storage under nitrogen in sealed ampoules at 0°, but such compounds should not be stored for longer than 14 days.

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Table 1. Reactions of 1-Diazo-2-oxo-3-phenylpropanes (**2**) with Hydrogen Halide

R	X	Type of Ketone obtained	Method[a]	m.p. or b.p.	(Lit. value)	Chemical Shift (δ)[b]
4-NO_2	Cl	**1**	**A, B**	m.p. 90–91°	(91–92°)[4]	3.60[c]
2,4-$(NO_2)_2$	Br	**1**	**A, B**	m.p. 100–101°	(96–97°)[3]	3.40
2,4-$(NO_2)_2$	Cl	**1**	**A, B**	m.p. 109–110°		3.45
4-Cl	Cl	**1**	**A, B**	m.p. 62–63°	(155–160°/6 mm)[5]	4.10
4-CH_3	Br	**1**	**A, B**	m.p. 49–50°		4.06
4-CH_3	Cl	**1**	**A, B**	m.p. 56–57°	(135–140°/7 mm)[5]	4.09
H	Cl	**1**	**A, B**	m.p. 70–72°	(72–73°)[6]	4.09
H	Br	**1**	**A, B**	b.p. 82–87°/0.1 mm	(88–90.5°/0.15 mm)[2]	4.05
H	Br	**3**	**B, C**	b.p. 90–95°/1.0 mm	(122–126°/8 mm)[2]	5.30
4-OCH_3	Br	**1**	**A**	m.p. 64–66°		4.06
4-OCH_3	Br	**3**	**B, C**	m.p. 49–50°	(47–52°)[7]	5.30
4-OCH_3	Cl	**1**	**A**	m.p. 40–41°	(161–163°/15 mm)[5]	4.08
4-OCH_3	Cl	**3**	**B, C**	b.p. 110–113°/0.5 mm		5.33
3,4-$(OCH_3)_2$	Cl	**1**	**A**	m.p. 77–78°		4.12
3,4-$(OCH_3)_2$	Cl	**3**	**B, C**	b.p. 140–142°/0.8 mm		5.34

[a] Methods **A**, **B**, and **C** refer to the conditions shown in the above reaction scheme.

[b] Benzyl protons (singlet) for type **1** ketones, benzylic proton (singlet) for type **3** ketones. All in $CDCl_3$ against tetramethylsilane at 100 MHz.

[c] Measured in acetone-d_6.

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