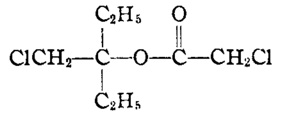
[Contribution from the Department of Chemistry of the University of Rochester]

A New Method for the Synthesis of α-Chloroketones

By J. F. Bunnett and D. S. Tarbell

As intermediates in the synthesis of some 4-alkyl-2-mercaptothiazoles, chloromethyl alkyl ketones were required. Ketones of this type are most commonly obtained by treating diazomethyl ketones, from the reaction of acid chlorides with diazomethane, with dry hydrogen chloride.[1] While this synthesis gives good yields, its application on a large scale is not attractive, due to the treacherous character of diazomethane. Furthermore, for the synthesis of chloromethyl alkyl ketones in which the alkyl group is a long straight chain, this method is readily applicable only to the preparation of those compounds having an uneven number of carbon atoms,[2] the available starting materials being acids with an even number of carbon atoms.

It appeared that chloromethyl alkyl ketones might be obtained more easily from the ketone synthesis of Gilman and Nelson[3] which involves the reaction of an acid chloride with an organocadmium compound. This synthesis has been widely used in recent years, usually with good results, for the preparation of a variety of ketones[4] not including, however, any α-chloroketones. We had some doubt as to whether the synthesis could be applied to the preparation of α-chloroketones, for Blaise[5] reported that ethylzinc iodide and chloroacetyl chloride gave not the expected 1-chlorobutanone-2, but rather the ester I which resulted from addition of a second mole of organozinc compound to the carbonyl group of the chloroketone, followed by esterification.



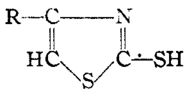
$$ClCH_2-\overset{C_2H_5}{\underset{C_2H_5}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_2Cl$$

I

However, we found that the reaction of alkyl cadmium compounds with chloroacetyl chloride resulted in the corresponding alkyl chloromethyl ketones in fair yields. The following ketones were prepared in the yields indicated: 1-chlorohexanone-2, 22–29%, 1-chloroheptanone-2, 24%, 1-chlorotetradecanone-2, 8–18%, 1-chlorohexadecanone-2, > 22%, phenacyl chloride, very poor yield. The reaction of di-(n-dodecyl)-cadmium with α-chloropropionyl chloride gave a 13% yield of 2-chloropentadecanone-3 and the reaction is much less satisfactory than the one with chloroacetyl chloride.

The lesser nucleophilic reactivity of organocadmium compared to organozinc compounds is emphasized by their reactions with chloroacetyl chloride. It is clear that the α-chloroketones initially formed in both cases possess an especially active carbonyl group. The addition of both organozinc[5] and organocadmium[3] compounds to other activated carbonyl groups is recorded in the literature, and such a secondary reaction probably limited the yields in the preparations reported here. We made no attempts to identify side-products of the reactions.

The desired mercaptothiazoles, II and III, were obtained by the condensation of 1-chlorotetradecanone-2 and 1-chlorohexadecanone-2, respectively, with ammonium dithiocarbamate in boiling ethanol.[6]



II, R = n-$C_{12}H_{25}$
III, R = n-$C_{14}H_{29}$

The phenyl sulfones, formed by treating the chloroketones with sodium benzenesulfinate in alcohol,[7] were found to be satisfactory derivatives of 1-chlorotetradecanone-2, 1-chlorohexadecanone-2, and 2-chloropentadecanone-3. However, the sulfone from 1-chlorohexanone-2 was an oil, as were its 2,4-dinitrophenylhydrazone and β-naphthoxy derivative. However, this ketone and 1-chloroheptanone-2 both gave solid phthalimido derivatives upon reaction with potassium phthalimide.[8]

Experimental[9]

Anhydrous cadmium chloride was prepared by fusing (hood) the c. p. dihydrate in small batches in an evaporating dish over a Meker flame. After being allowed to cool in a desiccator, the fused mass was freed from the dish (a few taps were usually sufficient), broken into large chunks, and so stored in a tightly capped bottle. Just before being introduced into the reaction mixture, the cadmium chloride was finely ground in a porcelain mortar.

Ammonium Dithiocarbamate.—The preparative directions of Miller[10] were followed.

1-Chlorohexanone-2.—The procedure followed in preparing the various chloroketones was essentially uniform, and is described in detail only for 1-chlorohexanone-2. In every case, 1.1 molecular proportion of alkyl bromide was

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(1) Bradley and Schwarzenbach, *J. Chem. Soc.*, 2904 (1928); Arndt and Amende, *Ber.*, **61**, 1122 (1928).

(2) Jensen and Kjaer, *Dansk. Tids. Farm.*, **16**, 110 (1942): *C. A.*, **38**, 2326 (1944).

(3) Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

(4) *Cf.* Cason, This Journal, **64**, 1106 (1942); Cason and Prout, *ibid.*, **66**, 46 (1944); Suter and Weston, *ibid.*, **61**, 232 (1939); Hoehn and Moffett, *ibid.*, **67**, 740 (1945); Johnson and Offenhauer, *ibid.*, **67**, 1049 (1945).

(5) Blaise, *Compt. rend.*, **155**, 47 (1912); Blaise, *Bull. soc. chim.*, [4] **9**, I–XXVI (at p. 408) (1911).

(6) Miolati, *Gazz. chim. ital.*, **23**, I, 575 (1893); *Ber.*, **26** (ref.) 604 (1893).

(7) Otto and Otto, *J. prakt. Chem.*, [2] **36**, 403 (1887); McPhee and Klingsberg, This Journal, **66**, 1132 (1944).

(8) Gabriel and Pinkus, *Ber.*, **26**, 2197 (1893).

(9) Carbon–hydrogen analyses marked $^{(B)}$ by Mr. Robert Bauman, marked $^{(C)}$ by Mr. Carl Claus, and marked $^{(T)}$ by Dr. Carl Tiedcke, Laboratory of Microchemistry, New York City. All melting points corrected.

(10) Miller, *Contrib. Boyce Thompson Inst.*, **5**, 31 (1933).

used in preparing the Grignard reagent for each molecular proportion of magnesium (in order to ensure complete consumption of the magnesium). All yields are calculated on the basis of the amount of alkyl bromide used.

To a Grignard reagent prepared in the usual manner from 19.0 g. (0.775 mole) of magnesium turnings and 117.0 g. (0.855 mole) of *n*-butyl bromide, and cooled by an ice-bath, were added with stirring 81.0 g. (0.44 mole) of ground anhydrous cadmium chloride. The ice-bath was removed and the mixture allowed to warm to room temperature as it was stirred. A negative Gilman test[11] was obtained after fifty-seven minutes. To the mixture, again cooled by an ice-bath, was added with stirring 59 ml. (87.5 g., or 0.78 mole) of chloroacetyl chloride at a rate[12] sufficient for the heat of reaction to keep the ether at a gentle reflux. When, following addition, the reaction had subsided, the ice-bath was removed and when the mixture no longer refluxed spontaneously, refluxing was continued another half hour by external heating (water-bath). Hydrolysis was effected by the careful addition (with stirring) of dilute sulfuric acid to the ice-cold reaction mixture.

After hydrolysis, the ether layer was separated and washed in succession with 250-cc. portions of water, 5% sodium bicarbonate and water, and then dried over anhydrous sodium sulfate. Following removal of ether on the steam-bath, the product was distilled at 14 mm., the fractions boiling between 67 and 71° being collected as 1-chloro-hexanone-2. The yield was 25.2 g. (n^{24}D 1.4360) plus 4.9 g. (n^{24}D 1.4390).[13] This represents a 26% over-all yield.

1-Chloroheptanone-2.—The procedure described above was followed with the exception that the temperature of the reaction mixture was held at 0° during addition of all the chloroacetyl chloride. *n*-Amyl bromide (25.8 g.) and appropriate amounts of other reagents were used; two fractions of product, boiling between 80 and 82.5° at 12 mm., were collected as 1-chloroheptanone-2. The yield was 3.4 g. (n^{20}D 1.4371) plus 2.6 g. (n^{20}D 1.4423). McCusker and Vogt[14] reported for 1-chloroheptanone-2: n^{26}D 1.4387. This represents a 24% over-all yield.

1-Chlorotetradecanone-2.—In four runs according to the procedure described for 1-chlorohexanone-2, the yields of 1-chlorotetradecanone-2 were 8.4, 15.4, 18 and 18%. In a typical run, 102.2 g. of *n*-dodecyl bromide and proper amounts of other reagents were used. By distillation at 1 mm., the following fractions of product were collected:

Fraction	B. p., °C.	Wt., g.	n^{43}D
IV	125–133	3.7	1.4440
V	133–147	6.3	
VI	140–150	5.6	1.4473

Their combined weight is 15.6 g. (15.4%). On recrystallization of fraction V from petroleum ether (b. p. 30–40°), 3.05 g. of waxy leaflets, m. p. 40–42°, was recovered.

1-Chlorotetradecanone-2 was also prepared by carbonation of *n*-dodecylmagnesium bromide, treatment of the resulting tridecanoic acid[15] with thionyl chloride (to give the acid chloride), and treatment of the acid chloride with diazomethane followed by dry hydrogen chloride. The product, b. p. 126–128° (1 mm.), was recrystallized from methanol. The white plates obtained (by filtration at 0°) melted at 40.5–41.5°, had n^{45}D 1.4464 and gave no depression on mixed m. p. with the sample described in the preceding paragraph.

Anal. Calcd. for $C_{14}H_{27}OCl$: C, 68.12; H, 11.03. Found:[B] C, 68.56; H, 11.31.

This ketone was further characterized by converting it to the phenyl sulfone, **1-benzenesulfonyltetradecanone-2,** by heating it with sodium benzenesulfinate in ethanol for an hour. The reaction mixture was poured into water, the product collected and recrystallized (using Norit) from petroleum ether (b. p. 60–70°); m. p. 70–71.5°. After two more recrystallizations from the same solvent, white needles, m. p. 71–71.5°, were obtained.

Anal. Calcd. for $C_{20}H_{32}O_3S$: C, 68.14; H, 9.15. Found:[T] C, 68.14; H, 9.17.

1-Chlorohexadecanone-2.—The usual procedure was followed, using 170 g. of *n*-tetradecyl bromide. An accident occurred in which about a fifth of the alkyl bromide spilled on the desk before it was added to the reaction mixture. The following fractions of product were obtained by distillation at 1 mm.:

Fraction	B. p., °C.	Wt., g.	
5	147–160	21.4	n^{44}D 1.4468
6	155–172	15.0	n^{44}D 1.4487
7	165–176	1.3	n^{40}D 1.4499

The combined fractions weigh 37.7 g. (22%).[16] Recrystallization from methanol yielded 22.9 g. (14.5%)[16] of flaky leaflets, m. p. 48–52°. Two more recrystallizations raised the melting point to 52–52.5°.

Anal. Calcd. for $C_{16}H_{31}OCl$: C, 69.91; H, 11.37. Found:[C] C, 69.45; H, 11.44.

The phenyl sulfone, **1-benzenesulfonylhexadecanone-2,** resulted in 72% yield from treatment of the ketone with sodium benzenesulfinate in ethanol. By recrystallization from petroleum ether (b. p. 60–70°) white crystals, m. p. 78–79°, were obtained.

Anal. Calcd. for $C_{22}H_{36}O_3S$: C, 69.43; H, 9.54. Found:[C] C, 69.51; H, 9.45.

2-Chloropentadecanone-3.—The method described for 1-chlorohexanone-2 was followed, using 33.1 g. of *n*-dodecyl bromide, 15.4 g. of α-chloropropionyl chloride, and appropriate amounts of other reagents. The product was distilled at 2 mm., and the fractions boiling between 98 and 167° and having n^{22}D between 1.4520 and 1.4555 were combined (total weight, 13.5 g.) and redistilled at 3 mm. Six fractions from the latter distillation, boiling between 129 and 150°, having nD between 1.4510 and 1.4519, and weighing, in all, 4.4 g. (13%) were collected as 2-chloropentadecanone-3. A middle fraction (liquid at room temperature but solid at 0°) was recrystallized twice from methanol (filtration at 0°). The purified ketone (still liquid at room temperature; n^{23}D 1.4513) was dried and analyzed.

Anal. Calcd. for $C_{15}H_{29}OCl$: C, 69.06; H, 11.21. Found:[C] C, 68.53; H, 10.88.

The phenyl sulfone, **2-benzenesulfonylpentadecanone-3,** was obtained after recrystallization from petroleum ether (b. p. 30–40°) as white crystals, m. p. 65–66°.

Anal. Calcd. for $C_{21}H_{34}O_3S$: C, 68.81; H, 9.35. Found:[C] C, 68.94; H, 9.26.

4-Tetradecyl-2-mercaptothiazole, III.—A solution of 1.52 g. of 1-chlorohexadecanone-2 and 1 g. of ammonium dithiocarbamate in 10 cc. of methanol was refluxed on the steam-bath. After twenty-five minutes, another half gram of ammonium dithiocarbamate was added and refluxing continued another twenty minutes before the addition of water caused the separation of an oil which solidified in the refrigerator. The solid was recrystallized from petroleum ether (b. p. 60–70°) whereupon 0.89 g. (52%) of well-defined crystals was obtained. Three more recrystallizations from the same solvent yielded creamy-white plates, m. p. 78–79°.

Anal. Calcd. for $C_{17}H_{31}NS_2$: C, 65.12; H, 9.97. Found:[C] C, 65.03; H, 9.77.

4-Dodecyl-2-mercaptothiazole, III.—Preparation by the method described above yielded 45% of white crystals, m. p. 68.5–70°.

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(11) Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

(12) The chloroacetyl chloride is added very slowly at first, and not in great amount until reaction has been initiated in the flask. As reaction starts, the mixture changes from gray to a yellowish-green. Usually a yellow precipitate forms as the reaction proceeds.

(13) Verbanc and Hennion, THIS JOURNAL, **60**, 1711 (1938), reported n^{24}D 1.4370 for 1-chlorohexanone-2.

(14) McCusker and Vogt, *ibid.*, **59**, 1307 (1937).

(15) Fierz-David and Kuster, *Helv. Chim. Acta*, **22**, 87 (1939).

(16) On basis that all the *n*-tetradecyl bromide had been used in the reaction.

Anal. Calcd. for $C_{15}H_{27}NS_2$: C, 63.10; H, 9.53; mercaptan sulfur, 11.23. Found:[B] C, 63.40; H, 9.60; mercaptan sulfur,[17] 10.9.

1-Phthalimidohexanone-2.—Potassium phthalimide (2.0 g.) and 1.4 g. of 1-chlorohexanone-2 were mixed with 15 cc. of 95% ethanol, and the mixture refluxed for seventy minutes. The solution was decanted from the grainy deposit of potassium chloride, evaporated nearly to dryness, and the residue extracted twice with petroleum ether (b. p. 30–40°). Cooling the extracts in the refrigerator caused 0.36 g. (15%) of white needles, m. p. 63–65°, to separate. Recrystallization raised the melting point to 69–69.5°.

Anal. Calcd. for $C_{14}H_{15}O_3N$: C, 68.55; H, 6.16. Found:[C] C, 69.02; H, 6.13.

This compound was also prepared (in 29% yield) by heating 1-chlorohexanone-2 and a slight excess of potassium phthalimide without solvent at 120–130° for half an hour.

1-Phthalimidoheptanone-2.—By the method described above, there was obtained a 13% yield of this derivative which, after recrystallization from petroleum ether (b. p. 40–60°), melted at 62.5–63.5°.

Anal. Calcd. for $C_{15}H_{17}O_3N$: C, 69.41; H, 6.61. Found:[C] C, 69.19; H, 6.44.

Summary

1. α-Chloroketones have been obtained in moderate yield by the reaction of alkylcadmium compounds with chloroacetyl chloride and α-chloropropionyl chloride.

2. The data obtained emphasize the lesser nucleophilic reactivity of organocadmium as compared to organozinc compounds.

3. The preparation of two 4-alkyl-2-mercaptothiazoles is described.

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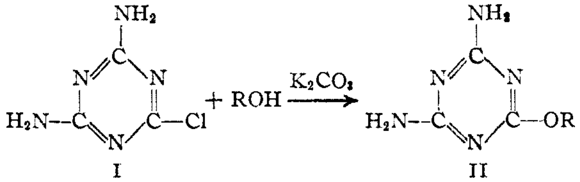
[17] Mercaptan sulfur analysis through courtesy of Dr. W. C. MacTavish, New York University.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & COMPANY]

Alkoxy-*s*-Triazines

BY JOHN CONTROULIS[1] AND C. K. BANKS

In a previous study of the reaction of 2-chloro-4,6-diamino-*s*-triazine (I) with arylarsonic acids,[1a] the reaction between *p*-hydroxybenzenearsonic acid and I was attempted. The first medium employed was dilute hydrochloric acid but the only product isolated was ammeline, 2-hydroxy-4,6-diamino-*s*-triazine. When this same reaction was carried out in dry cellosolve with an equivalent of potassium carbonate, an unexpected product was obtained. Instead of the phenolic hydroxyl group of the benzenearsonic acid taking part in the reaction, the hydroxyl group of the cellosolve reacted with the triazine (I) yielding 2-β-ethoxyethoxy-4,6-diamino-*s*-triazine as indicated in the type reaction



I II

The arsonic acid was recovered unchanged.

Due to the pharmacological properties exhibited by the triazine arsenicals,[1a] it was thought advisable to prepare a series of compounds of the same type as II. The extent of the interaction of I with various alcohols in the presence of potassium carbonate was unsatisfactory both with respect to the yield of product and the time of reaction. The conditions of the classical Williamson reaction were then employed and found to be suitable. The sodium alcoholate was prepared in an excess of the alcohol and then the chloro-triazine was added. Refluxing this mixture for one to five hours was sufficient to obtain complete reaction. In an instance where an excess of the alcohol was not available, a second procedure was employed wherein an equivalent of the alcohol dissolved in xylene was treated with sodium. When the metal had dissolved, the halide was added and refluxing effected to cause the elimination of sodium chloride. The same products were also obtained when alcoholic suspensions of halotriazines were saturated with dry hydrogen chloride. However, the products obtained by this method were purified with greater difficulty.

Of the various types of alcohols employed it was found that the *iso*- and *sec*-alkyl alcohols took part in the reaction as readily as the primary alcohols. However, no ether type product was obtained from the action of the halotriazine on sodium *t*-butylate. This was also the case with the sodium derivatives of benzhydrol, fluorenol, xanthydrol and menthol. Whether or not this phenomenon was due to steric influence was not determined.

Table I lists the compounds prepared and their physical constants. 2-Ethoxy-4,6-diamino-*s*-triazine was prepared by Hofmann[2] by the action of ammonia on the triethyl ester of cyanuric acid. The melting point he observed was 190–200°, the considerable range probably being due to the presence of ammeline, which has a high decomposition point. The occurrence of this impurity in the crude alkoxy-triazines listed in this paper caused an elevation of the melting points of these

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[1a] Banks, Gruhzit, Tillitson and Controulis, THIS JOURNAL, **66**, 1771 (1944).

[2] Hofmann, *Ber.*, **19**, 2080 (1886).