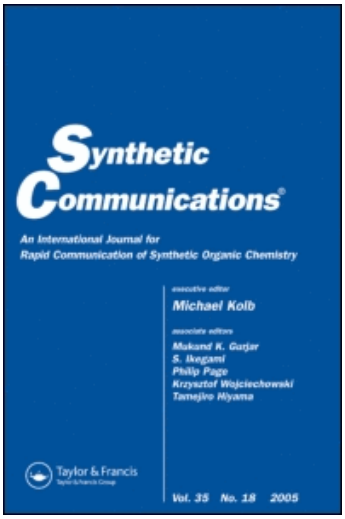

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SELECTIVE PREPARATION OF α,α-DICHLOROKETONES WITH COPPER(II) CHLORIDE

José Arimateia Nobrega[a]; Simone Maria C. Gonçalves[a]; Clovis Peppe[b]
[a] Departamento de Química Fundamental, Universidade Federal de Pernambuco, UFPE, Recife, PE, Brazil [b] Laboratório de Materiais Inorgânicos, Departamento de Química, Universidade Federal de Santa Maria, UFSM, Santa Maria, RS, Brazil

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SELECTIVE PREPARATION OF α,α-DICHLOROKETONES WITH COPPER(II) CHLORIDE

José Arimateia Nobrega,[1]
Simone Maria C. Gonçalves,[1] and Clovis Peppe[2,*]

[1]Departamento de Química Fundamental, Universidade Federal de Pernambuco, UFPE, Recife-PE, Brazil, 50670-901
[2]Laboratório de Materiais Inorgânicos, Departamento de Química, Universidade Federal de Santa Maria, UFSM, Santa Maria-RS, Brazil, 97105-900

ABSTRACT

Aryl and enolizable alkyl ketones react with copper(II) chloride in dimethylformamide to produce the corresponding α,α-dichloroketone in high yields. Remarkable qualities of the process are high selectivity towards these substrates, undetected polychlorinated by-products, easy work-up, commercially available reagents and HCl as the only waste stream.

Key Words: Dichloroketones; Dichlorination; Copper(II) chloride

*Corresponding author. E-mail: peppe@quimica.ufsm.br

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The use of α,α-dihalogenoketones as building blocks in organic synthesis has been investigated scarcely. A few reports[1,2] established that these compounds present very interesting chemical properties. The electrochemical reduction of α,α-dibromoacetophenone led to the simultaneous production of (*E*)-4,4-dibromo-1,3-diphenyl-2,3-epoxybutan-1-one and *trans*-1,2,3-tribenzoylcyclopropane, via anionic and carbene intermediates, respectively. The reaction of α,α-dichloroacetophenone with substituted benzaldehydes, under the Darzens conditions, produced the corresponding 1-phenyl-2-chloro-3-aryl-2,3-epoxy-1-propanone and 1-phenyl-3-aryl-3-chloro-1,2-propanedione, the latter as the result of the epoxide ring-opening.[2]

Despite the relevance of these results, the use of α,α-dihalogenoketones in organic synthesis still remains unexplored. This is probably due to the lack of a convenient synthetic protocol to prepare them, particularly the α,α-dichloro compounds, which have been synthesized from acetylenes and *N*-chlorosuccinimide.[3] Alternative procedures starting with carbonyl precursors, are controlled addition of gaseous Cl_2, in formic acid containing HCl as catalyst;[4] reaction with sulfuryl chloride;[5] and with an ammonium salt of tetrachloroiodate.[6] Simultaneous formation of polychlorinated by-products seems to be the major limitation associated with some[4,5] of the latter methods.

CuX_2 (X = Cl, Br) compounds have been used to produce the corresponding monohalogeno derivatives of silyl enol ethers,[7] enol esters,[8] and ketones.[9,10] The latter reaction is known as the Kosower method. We now report that it is possible to adjust the condition of the Kosower reaction to produce α,α-dichloroketones from the corresponding ketones,[11,12] with no signs of polychlorinated by-products, overcoming the major limitation associated to some of the synthetic routes discussed above.

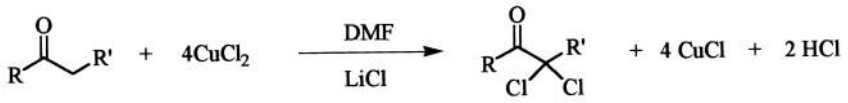

Table 1 shows that a variety of aryl and enolizable alkyl ketones were selectively transformed into their α,α-dichloro derivatives in good to excellent yields. An insight on the scope and generality of the present method was obtained by studying the reactions with substituted acetophenones at the aryl and alkyl portions of the molecules. We have observed that there is no significant difference in reactivity between acetophenone (Entry 1) and its derivatives containing electron donating (Entries 2–6) or electron withdrawing groups (Entries 7–8). Substitution at the alkyl portion produced similar

Table 1. Selective Preparation of α,α-Dichloroketones with Copper(II) Chloride

Entry	R	R′	Time (h)	Yield (%)
1	C_6H_5	H	4	76
2	4-CH_3-C_6H_5	H	5	70
3	4-C_6H_5-C_6H_4	H	5	71
4	4-MeO-C_6H_5	H	4	82
5	3,4-OCH_2O-C_6H_5[a]	H	4	80
6	2-C_4H_3S[b]	H	5	74
7	4-Cl-C_6H_5	H	4	86
8	4-F-C_6H_5	H	4	90
9	C_6H_5	CH_3	6	70
10	C_6H_5	C_6H_5	5	80
11	CH_3	C_6H_5	2	65
12	CH_3CH_2O	$C(=O)CH_3$	2	94
13	(CH_2)[c]		28	N.R.

[a]3′,4′-(Methylenedioxy)acetophenone; [b]2′-Acetyl-thiophene; [c]Cyclohexanone, N.R = No reaction was observed.

results. Thus, propiophenone (Entry 9) and 2-phenylacetophenone (Entry 10) produced comparable yields than acetophenone, under similar reaction conditions.

We have examined also the reaction between $CuCl_2$ with alkyl ketones. We first note that we fail to observe the formation of the α,α-dichloro derivative from cyclohexanone (Entry 13), even after a long period of reflux. But, the highly enolizable 1-phenyl-propan-2-one (Entry 11) and methyl acetoacetate react considerably faster than their aryl analogues, and no chlorination on the methyl groups of the molecules was observed.

We, therefore, conclude that this modification introduced in the Kosower method is highly efficient for the selective preparation of α,α-dichloroketones directly from their aryl and highly enolizable alkyl carbonyl precursors. Special advantages associated with it when compared to the previous methodologies are the use of non-toxic and commercially available starting materials, easy work-up and high yields.

Selective preparation of α,α-dichloroketones with copper(II) chloride. Experimental procedure: $CuCl_2 \cdot 2H_2O$ (2.00 g, 11.73 mmol) and LiCl (0.50 g, 11.73 mmol) were dissolved in DMF (9 mL) in a two-neck round-bottomed flask equipped with a reflux condenser. To this solution, the corresponding ketone (1.95 mmol) was added and the mixture heated (90°C) under magnetic stirring for the appropriated time (Table 1). The mixture was

cooled to room temperature, CH_2Cl_2 (50 mL) added, and the organic solution washed with H_2O (40 mL). The phases were separated; the aqueous phase was washed with CH_2Cl_2 (50 mL). The two CH_2Cl_2 portions were combined and washed with H_2O (40 mL) to ensure complete removal of DMF. The organic extract was dried ($MgSO_4$), filtered and evaporated to dryness to leave the α,α-dichloroketone, which was purified by column chromatography on silica gel (hexane:ethyl acetate), and characterized by: NMR (^1H, 300 MHz in $CDCl_3$ solutions and ^{13}C, 75.4 MHz, $CDCl_3$ solutions) in a VARIAN Unityplus 300 instrument; IR spectroscopy (neat samples between KBr plates) in a BOMEN 1,45 instrument; mass spectrometry ($CHCl_3$ solutions) obtained on a FINNIGAN GCQ instrument operating at 70 eV; and microanalysis obtained on a CHNS-O 1110 from CE Instruments. Melting points were determined with a Micro Quimica MQAPF-301 instrument and are uncorrected. Boiling points are uncorrected. Yields and other conditions are given in Table 1.

Entry 1 (2,2-dichloro-acetophenone): Boiling point: 58–60°C (1.1 mm Hg), Lit.[6] 243°C (760 mm Hg); % calculated (found) for $C_8H_6Cl_2O$: C, 50.82 (50.69); H, 3.19 (3.11); ^1H NMR: 6.67 (1H, s, $CHCl_2$), 8.1–7.5 (5H, m, Arom.); ^{13}C NMR: 67.75 ($CHCl_2$), 128.90 ($C_{ar}H$), 129.71 ($C_{ar}H$), 131.30 ($C1'_{ar.}$), 134.53 ($C2'_{ar}H$ and $C5'_{ar}H$), 185.88 (C=O); MS, *m/z* [ion, %]: 189/191/193 [$(M+1)^+$, 10], 153/155 [$(M-Cl)^+$, 5], 105 [$(M-CHCl_2)^+$, 100]; IR (cm^{-1}): 3064.64, 2922.97, 1707.32, 1596.29, 1449.46, 814.31, 686.26.

Entry 2 (2,2-dichloro-4′-methyl-acetophenone): Melting point: 52–53°C, Lit.[6] 53.5–54°C; % calculated (found) for $C_9H_8Cl_2O$: C, 53.23 (53.38); H, 3.97 (3.81); ^1H NMR: 2.42 (3H, s, CH_3), 6.66 (1H,s, $CHCl_2$), 7.30 (2H, d, $J = 8.2$ Hz, CH_{ar}), 7.95 (2H, d, $J = 8.2$ Hz, CH_{ar}); ^{13}C NMR: 21.80 ($ArCH_3$), 67.79 ($CHCl_2$), 128.70 ($C1'_{ar}$), 129.60 ($C_{ar}H$), 129.82 ($C_{ar}H$), 145.83 ($C4'_{ar}$), 185.54 (C=O); MS, *m/z* [ion, %]: 202/204/206 [$M^{+\cdot}$, 10], 167/169 [$(M-Cl)^+$, 5], 119 [$(M-CHCl_2)^+$, 100], 91 [$C_7H_7^+$, 42]; IR (cm^{-1}): 3044.34, 2928.67, 1710.32, 1591.22, 1453.45, 817.32, 680.35.

Entry 3 (2,2-dichloro-4′-phenyl-acetophenone): Melting point: 85–87°C; % calculated (found) for $C_{14}H_{10}Cl_2O$: C, 63.42 (63.58); H, 3.80 (3.72); ^1H NMR: 6.70 (1H, s, $CHCl_2$), 7.44–8.17 (9H, m, CH_{ar}); ^{13}C NMR: 67.86 ($CHCl_2$), 127.29 ($C_{ar}H$), 127.46 ($C_{ar}H$), 128.66 ($C_{ar}H$), 129.05 ($C_{ar}H$), 129.88 (C_{ar}), 130.36 ($C_{ar}H$), 139.33 (C_{ar}), 147.25 (C_{ar}), 185.52 (C=O); MS, *m/z* [ion, %]: 264/266/268 [$M^{+\cdot}$, 5], 229/231 [$(M-Cl)^+$, 7], 181 [$(M-CHCl_2)^+$, 100], 153 [C_6H_5-$C_6H_4^+$, 26]; IR (cm^{-1}): 3011.36, 1691.79, 1602.04, 1406.42, 1235.97, 855.19.

Entry 4 (2,2-dichloro-4′-methoxy-acetophenone): Melting point: 77–79°C, Lit.[6] 77–78°C; % calculated (found) for $C_9H_8Cl_2O_2$: C, 49.34 (49.26); H, 3.68 (3.59); ^1H NMR: 3.87 (3H, s, OCH_3), 6.63 (1H, s,

$CHCl_2$), 6.95 (2H, d, $J=9$ Hz, C2′$_{ar}$H and C6′$_{ar}$H), 8.04 (2H, d, $J=9$ Hz, C3′$_{ar}$H and C5′$_{ar}$H); ^{13}C NMR: 55.61 (OCH_3), 67.82 ($CHCl_2$), 114.16 (C2′$_{ar}$H and C6′$_{ar}$H), 123.83 (C1′$_{ar}$), 132.23 (C3′$_{ar}$H and C5′$_{ar}$H), 164.57 (C4′$_{ar}$-OMe), 188.55 (C=O); MS, *m/z* [ion, %]: 218/220/222 [$M^{+\cdot}$, 3], 135 [$(M-CHCl_2)^+$, 100], 107 [$CH_3OC_6H_4^+$, 10]; IR (cm^{-1}): 3029.81, 2980.86, 1682.93, 1237.60, 1177.63, 847.91, 604.08.

Entry 5 (2,2-dichloro-3′,4′-methylenedioxy-acetophenone): Melting point: 82–84°C; % calculated (found) for $C_9H_6Cl_2O_3$: C, 46.38 (46.32); H, 2.59 (2.41); ^{1}H NMR: 6.06 (2H, s, O-CH_2-O), 6.60 (1H, s, $CHCl_2$), 6.87 (1H, d, $J=8.2$ Hz, C5′$_{ar}$H), 7.51 (1H, d, $J=2$ Hz, C2′$_{ar}$H), 7.69 (1H, dd, $J=8.2$ Hz, 2 Hz, C6′$_{ar}$H); ^{13}C NMR: 67.27 ($CHCl_2$), 102.25 (O-CH_2-O), 109.31 (C2′$_{ar}$H), 108.22 (C5′$_{ar}$H), 125.59 (C1′$_{ar}$), 126.50 (C6′$_{ar}$H), 148.42 (C3′$_{ar}$-O), 153.07 (C4′$_{ar}$-O), 184.24 (C=O); MS, *m/z* [ion, %]: 232/234/236 [$M^{+\cdot}$, 10], 197/199 [$(M-Cl)^+$, 2], 149 [$(M-CHCl_2)^+$, 100], 121 [$CH_2O_2C_6H_3^+$, 15]; IR (cm^{-1}): 3023.42, 2920.86, 1681.65, 1601.65, 1446.18, 1251.35, 1034.63, 656.88.

Entry 6 (2′-acetyl-2,2-dichloro-thiophene): Boiling point: 85–87°C (0.7 mm Hg); % calculated (found) for $C_6H_4Cl_2OS$: C, 36.94 (36.83); H, 2.05 (2.02); S, 16.44 (16.39); ^{1}H NMR: 6.52 (1H, s, $CHCl_2$), 7.14 (1H, dd, $J=4$ Hz, $J=5$ Hz, C4′$_{ar}$H), 7.74 (1H, d, $J=5$ Hz, C3′$_{ar}$H), 7.92 (1H, d, $J=4$ Hz, C5′$_{ar}$H); ^{13}C NMR: 67.76 ($CHCl_2$), 128.54 (C4′$_{ar}$H), 134.77 (C3′$_{ar}$H), 136.45 (C5′$_{ar}$H), 136.93 (C2′$_{ar}$), 179.53 (C=O); IR (cm^{-1}): 3102.40, 1682.41, 1515.16, 1411.28, 1356.71, 1244.15, 1217.88, 1066.41, 804.93, 727.10, 667.61.

Entry 7 (2,2,4′-trichloro-acetophenone): Melting point: 61–63°C, Lit.[6] 60–61.5°C; % calculated (found) for $C_8H_5Cl_3O$: C, 42.99 (42.88); H, 2.25 (2.31); ^{1}H NMR: 6.58 (1H, s, $CHCl_2$), 7.47 (2H, d, $J=8.8$ Hz, C2′$_{ar}$H and C6′$_{ar}$H), 8.02 (2H, d, $J=8.8$ Hz, C3′$_{ar}$H and C5′$_{ar}$H); ^{13}C NMR: 67.76 ($CHCl_2$), 129.25 (C_{ar}H), 129.42 (C1′$_{ar}$), 131.20 (C_{ar}H), 141.19 (C4′$_{ar}$Cl), 184.86 (C=O); MS, *m/z* [ion, %]: 223/225/227/229 [$(M+1)^+$, 5], 187/189/191 [$(M-Cl)^+$, 3], 139/141 [$(M-CHCl_2)^+$, 100]; IR (cm^{-1}): 3027.57, 1706.30, 1592.32, 1402.64, 1092.93, 848.78, 786.85.

Entry 8 (2,2-dichloro-4′-fluoro-acetophenone): Boiling point: 82–84°C (1.9 mm Hg); % calculated (found) for $C_8H_5Cl_2FO$: C, 46.41 (46.49); H, 2.43 (2.34); ^{1}H NMR: 6.59 (1H, s, $CHCl_2$), 7.18 (2H, dd, $J_{H-F}=8.2$ Hz, $J_{H-H}=8.6$ Hz, C3′$_{ar}$H and C5′$_{ar}$H), 8.13 (2H, dd, $J_{H-F}=5.4$ Hz, $J_{H-H}=8.6$ Hz, C2′$_{ar}$H and C6′$_{ar}$H); ^{13}C NMR: 67.78 ($CHCl_2$), 116.22 (d, $J=22$ Hz, C3′$_{ar}$ and C5′$_{ar}$), 132.90 (d, $J=9.5$ Hz, C2′$_{ar}$ and C6′$_{ar}$), 127.52 (C1′$_{ar}$), 166.41 (d, J = 257 Hz, C4′$_{ar}$), 184.54 (C=O); MS, *m/z* [ion, %]: 207/209/211 [$(M+1)^+$, 6], 171/173 [$(M-Cl)^+$, 3], 123 [$(M-CHCl_2)^+$, 100], 95 [$FC_6H_4^+$, 36]; IR (cm^{-1}): 3009.10, 1708.58, 1598.45, 1411.64, 1224.73, 853.42.

Entry 9 (2,2-dichloro-propiophenone): Boiling point: 69–71°C (2.6 mm Hg); % calculated (found) for $C_9H_8Cl_2O$: C, 53.23 (53.38); H, 3.97 (3.85); ^{1}H NMR: 2.34 (3H, s, CH_3), 7.37–7.58 (3H, m), 8.29–8.34 (2H, m); ^{13}C NMR: 34.24 (CH_3), 82.68 (CCl_2), 128.01 ($C_{ar}H$), 131.15 ($C_{ar}H$), 132.05 ($C1'_{ar}$), 133.57 ($C4'_{ar}H$), 188.05 (C=O); MS, *m/z* [ion, %]: 202/204/206 [$M^{+\cdot}$, 12], 167/169 [$(M-Cl)^+$, 7], 105 [$(M-C(CH_3)Cl_2)^+$, 100], 77 [$C_6H_5^+$, 46]; IR (cm^{-1}): 3064.40, 2996.53, 1693.32, 1598.72, 1448.27, 1258.71, 668.72.

Entry 10 (2,2-dicloro-2-phenyl-acetophenone): Melting point: 70–72°C; % calculated (found) for $C_{14}H_{10}Cl_2O$: C, 63.42 (63.36); H, 3.80 (3.85); ^{1}H NMR: 7.28–7.81 (m); ^{13}C NMR: 89.89 (CCl_2Ph), 125.93 ($C_{ar}H$), 128.06 ($C_{ar}H$), 128.93 ($C_{ar}H$), 129.82 ($C_{ar}H$), 131.05 ($C_{ar}H$), 131.62 (C_{ar}-CO), 133.24 ($C_{ar}H$), 139.44 (C_{ar}-CCl_2), 186.59 (C=O); MS, *m/z* [ion, %]: 229/231 [$(M-Cl)^+$, 25], 194 [$(M-Cl_2)^{+\cdot}$, 12], 105 [$(M-CCl_2Ph)^+$, 100], 77 [$C_6H_5^+$, 45]; IR (cm^{-1}): 3071.18, 1701.64, 1594.93, 1446.63, 1232.21, 732.17.

Entry 11 (2,2-dichloro-2-phenyl-propanone): Boiling point: 52–54°C (0.7 mm Hg); % calculated (found) for $C_9H_8Cl_2O$: C, 53.23 (53.15); H, 3.97 (3.89); ^{1}H NMR: 2.31 (3H, s, CH_3), 7.39–7.63 (5H, m); ^{13}C NMR: 23.64 (CH_3), 90.40 (CCl_2Ph), 126.63 ($C_{ar}H$), 128.66 ($C_{ar}H$), 129.83 ($C_{ar}H$), 137.33 ($C1'_{ar}$), 193.52 (C=O); IR (cm^{-1}): 3058.72, 2986.76, 1737.42, 1447.51, 1169.82, 746.33.

Entry 12 (ethyl-2,2-dichloro-acetoacetate): Boiling point: 52–54°C (0.8 mm Hg); % calculated (found) for $C_6H_8Cl_2O_3$: C, 36.21 (36.16); H, 4.02 (3.95); ^{1}H NMR: 1.27 (3H, t, $J=7$ Hz, $CH_2\mathbf{CH_3}$), 2.45 (3H, s, CH_3), 4.35 (2H, q, $J=7$ Hz, $\mathbf{CH_2}CH_3$); ^{13}C NMR: 13.72 (CH_2-$\mathbf{CH_3}$), 23.41 ($\mathbf{CH_3}$-CO), 64.60 (O-CH_2), 81.83 (CCl_2), 163.25 ($\mathbf{C}O_2CH_2CH_3$), 191.30 (CH_3-$\mathbf{C}$=O); IR (cm^{-1}): 2988.45, 1740.37, 1360.42, 1299.88, 1241.16, 1166.31, 1040.94.

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REFERENCES

1. Batanero, B.; Pastor, G.; Barba, F. Electrochemical Reduction of 2,2-Dibromoacetophenone. Acta Chem. Scand. **1999**, *53*, 910–912.
2. Mamedov, V.A.; Litvinov, I.A.; Kataeva, O.N.; Rizvanov, I.K.; Nuretdinov, I.A. Darzens Reaction as a Convenient Method for the

Synthesis of α-Chloroketones, α-Chloroepoxides, and Symmetrically Substituted Dioxines. Monatsh Chem. **1994**, *125*, 1427–1435.

3. Reed, S.F. The Preparation of α,α-Dichloro Ketones. J. Org. Chem. **1965**, *30*, 2195–2198.
4. Falbe, J.; Schulzesteinen, J. α-Chlorinated Acetophenones. Ger. Patent 1,223,824, Sept. 1, 1966; Chem. Abstr. **1966**, *65*, 15277c.
5. Wyman, D.P.; Kaufman, P.R. The Chlorination of Active Hydrogen Compounds with Sulfuryl Chloride. J. Org. Chem. **1964**, *29*, 1956–1958.
6. Kakinami, T.; Urabe, Y.; Hermawan, I.; Yamanishi, H.; Okamoto, T.; Kajigaeshi, S. Halogenation Using Quaternary Ammonium Polyhalides. Dichlorination of Aromatic Acetyl Derivatives with Benzyltrimethylammonium Tetrachloroiodate. Bull. Chem. Soc. Jpn. **1992**, *65*, 2549–2551.
7. Larock, R.C. *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989; 369–380.
8. Shi, X.X.; Dai, L.X. Mild Halogenation of Stabilized Ester Enolates by Cupric Halides. J. Org. Chem. **1993**, *58*, 4596–4598.
9. Kosower, E.M.; Cole, W.J.; Wu, G.S.; Cardy, D.E.; Meisters, G.J. Halogenation with Copper(II). Saturated Ketones and Phenol. J. Org. Chem. **1963**, *28*, 630–633.
10. (a) King, L.C.; Ostrum, G.K. Selective Bromination with Copper(II) Bromide. J. Org. Chem. **1964**, *29*, 3459–3461; (b) Doifode, K.B.; Marathey, M.G. Reactions of Cupric Bromide in Dioxane. Formation of ω-Bromo-*o*-hydroxyacetophenone. J. Org. Chem. **1964**, *29*, 2025–2026.
11. Best yields were obtained in experiments conducted in the molar ratio $CuCl_2$: ketone of 6 : 1.
12. The choice of DMF as the solvent was crucial. Reactions do not occur in acetonitrile and 1,4-dioxane.

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