One-Step Preparation of Symmetrical 1,4-Diketones from α-Halo Ketones in the Presence of Zn-I_2 as a Condensation Agent

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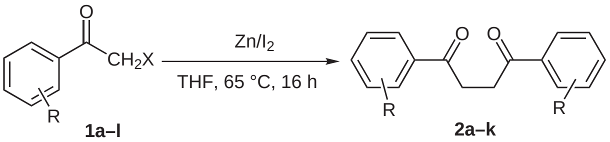
Abstract: Eleven 1,4-diphenylbutane-1,4-diones have been prepared in one step from the corresponding α-halo acetophenones under the action of Zn-I_2 as a condensation agent with moderate to high yields. The mechanistic pathway of the reaction can be explained by the Wurtz-like self-condensation of α-halo ketones. Similarly, 3-chloropentane-2,4-dione gave 3,4-diacetylhexane-2,5-dione, a Wurtz-like condensation product.

Key words: 1,4-Diketones, α-bromoketones, zinc

1,4-Diketones are important intermediates in the synthesis of five-membered carbocyclic[1] and heterocyclic[2] compounds, including the preparation of derivatives of terthiophene and other conjugated, five-membered heterocycles, which are being intensively investigated at present as monomers for electroconductive polymers.[3] Among the most convenient methods for the synthesis of symmetrical and asymmetrical 1,4-diketones,[4–17] the Michael–Stetter addition of aldehydes to α,β-unsaturated ketones,[8–12] as well as alkylation of stabilized alkaline metal enolates,[12–15] enamines[15,16] and tin enolates by α-halocarbonyl compounds should be mentioned.

In this paper, we present a new and simple procedure for the generation of twelve symmetrical 1,4-diketones directly from the corresponding α-halo ketones. The reaction of α-halo ketones **1a**–**m** with zinc dust in the presence of a small amount of I_2 at 65 °C gave the corresponding 1,4-diketones **2a**–**l**, Wurtz-like condensation products, in moderate to high yields (Scheme 1, Table 1).



Scheme 1

The synthesis of compound **2a** and similar products by different methods has been reported, but in only one[18] was the Zn-Cu couple (10 mol equiv) used in the presence of NaI (10 mol equiv). The reaction was carried out at high temperatures (90 and 170 °C), and resulted in 32 and 40% yields, respectively. Moreover, **2f** and **2i** were formed at 70 and 170 °C only in 32 and 25% yields, respectively.

In our method, zinc dust was used as a reagent in the presence of a small amount of iodine, while activated zinc dust (Zn-Cu/NaI) was used in the above method.[18] The reactions were performed at a lower temperature (65 °C), and resulted in higher yields of **2a** (67%), **2f** (98%) and **2i** (32%) (Table 1).

In the presence of a small amount of I_2, the reactions of α-halo ketones **1a**–**m** with zinc were completed at 65 °C in 16 hours. Very mild and almost neutral reaction conditions allowed us to obtain mostly good results by using different starting compounds containing halogen or methoxy functional groups. The structure of 1,4-diketones **2a**–**l** was elucidated from spectral data (NMR, IR, GC-MS, elemental analysis).

Some limitations of this procedure should also be mentioned. Moderate yields were obtained with electron-rich ketone (*p*-methoxy, **1i**) and *o*-substituted ketones **1d** and **1g**. Reductive removal of the functional groups from α-substituted carbonyl compounds is commonly known and a concerted mechanism has been suggested for this process.[19] The mechanism can be adopted to *o*-substituted ketones, as shown in Figure 1. The interaction of a substituent having lone electron pairs with solvent and bromide anion may lead to a coordinated Zn species, as seen in Figure 1. The low yields observed in *o*-substituted ketones may be caused by the formation of the probably stable intermediate complex **3** shown in Figure 1.

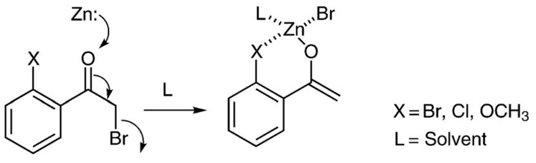


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Figure 1

The formation of 1,4-diketones can be reasonably explained by the intermediacy of the enolate-like anion **4** formed by the initial reduction of α-bromo ketones with zinc. The subsequent attack of enolate-like anion **4** on another α-carbon of ketone, bearing the bromine, leads to the Wurtz-type condensation products (Scheme 2).

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Table 1 1,4-Diketones Prepared from α-Halo Ketones

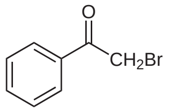
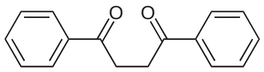
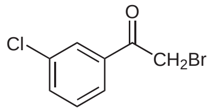
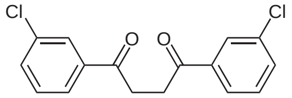
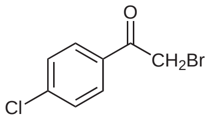
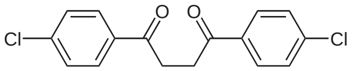
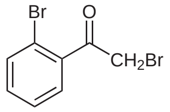
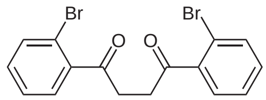
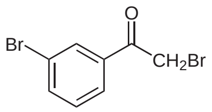
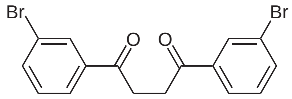
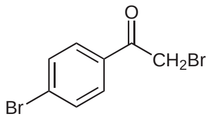
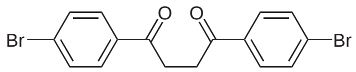
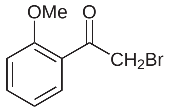
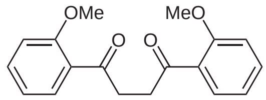
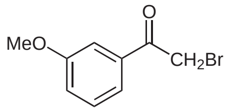
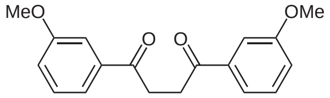
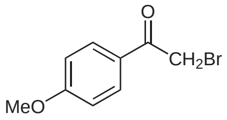
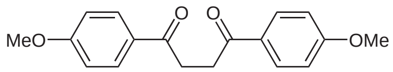
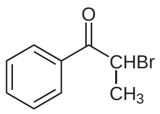
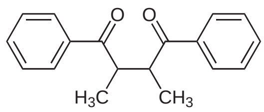
Entry	Reagents	Product	Yield (%)
1	 **1a**	 **2a**	67
2	 **1b**	 **2b**	89
3	 **1c**	 **2c**	97
4	 **1d**	 **2d**	29
5	 **1e**	 **2e**	51
6	 **1f**	 **2f**	96
7	 **1g**	 **2g**	26
8	 **1h**	 **2h**	60
9	 **1i**	 **2i**	32
10	 **1j**	 **2j**	79

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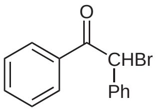
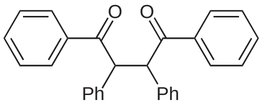
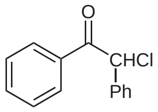
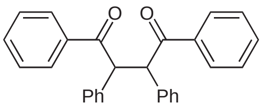
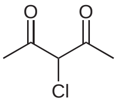
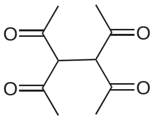
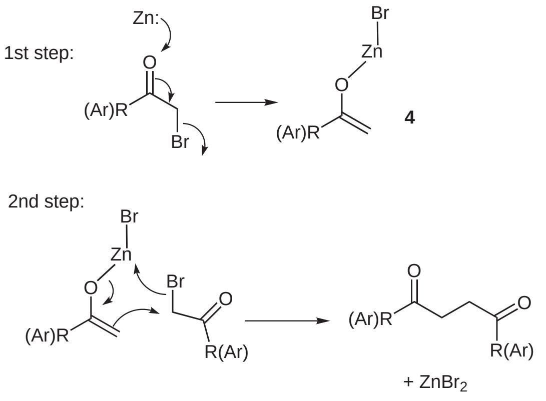
Table 1 1,4-Diketones Prepared from α-Halo Ketones (continued)

Entry	Reagents	Product	Yield (%)
11	 **1k**	 **2k**	87
12	 **1l**	 **2k**	98
13	 **1m**	 **2l**	68

The method described in this paper can be useful for the preparation of functionalized symmetrical 1,4-diketones under mild conditions.

2-Bromo-1-phenyl-ethanone (**1a**), 2-bromo-4′-chloroacetophenone (**1c**), 3-bromophenacyl bromide (**1e**), 4-bromophenacyl bromide (**1f**), 2-bromo-2′-methoxyacetophenone (**1g**), 2-bromo-3′-methoxyacetophenone (**1h**), 2-bromo-4′-methoxyacetophenone (**1i**), 2-bromopropiophenone (**1j**), 2-bromo-2-phenylacetophenone (**1k**), 2-chloro-2-phenylacetophenone (**1l**), and 3-chloropentane-2,4-dione (**1m**) are commercially available. Phenacyl bromides **1b**[20] and **1d**[21] were synthesized from *m*-chloroacetophenone and *o*-bromoacetophenone, respectively, by following a procedure described for phenacyl bromide.[22] Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. All solvents were dried and distilled by standard procedures. ^{1}H and ^{13}C NMR spectra were recorded on 200 (50) MHz Varian spectrometers, and are reported in δ units with TMS as internal standard. IR spectra were recorded as thin films or as solids in KBr pellets on a Perkin-Elmer 1717 FT spectrophotometer. MS spectra were performed on a Thermofinnigan Trace GC/Trace DSQ/A1300, (E.I. Quadrapole, 70 eV) equipped with an SGE-BPX5 MS capillary column (30 m × 0.25 mm i.d., 0.25 μm). The elemental analysis was performed using a CHNS-932 (LECO) analyzer. THF was distilled from potassium and benzophenone.



Scheme 2 Mechanism of formation of 1,4-diketones from α-halo ketones

1,4-Diketones; 1,4-Diphenyl-1,4-dione (2a); Typical Procedure

To a stirred solution of **1a** (3 g, 15 mmol) in anhyd THF (30 mL) was added Zn dust (1 g, 15 mmol) and a small amount of I_2. The reaction mixture was heated at a bath temperature of 65 °C for 16 h. After the mixture was cooled to r.t., the insoluble materials were separated by filtration. The filtrate was diluted with H_2O and extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ extracts were washed with H_2O, and dried ($MgSO_4$). After removal of solvent, recrystallization of the crude product from $CHCl_3$–*n*-hexane (8:2) gave **2a** (2.4 g, 67%); white needles; mp 143–145 °C (Lit.[23] mp 144–145 °C).

IR (KBr): 3081, 3070, 3050, 3025, 2965, 2904, 1677, 1577, 1446, 1353, 1222, 989, 761, 727, 690 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.46 (s, 4 H), 7.50 (m, 6 H), 8.04 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.60, 138.85, 135.09, 130.58, 130.11, 34.60.

MS: *m*/*z* (%) = 238 (M$^+$, 16), 220 (14), 133 (13), 105 (100), 77 (44).

1,4-Bis(3-chlorophenyl)butane-1,4-dione (2b)

Yield: 89%: colorless crystals; mp 142 °C ($CHCl_3$) (Lit.[24] mp 142–143 °C).

IR (KBr): 3097, 3073, 3027, 2942, 2911, 1675, 1571, 1556, 1432, 1274, 1187, 815, 736, 680 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.99 (m, 2 H), 7.91 (m, 2 H), 7.56 (m, 2 H), 7.43 (m, 2 H), 3.43 (s, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.13, 140.20, 136.99, 135.14, 131.97, 130.26, 128.19, 34.61.

MS: *m*/*z* (%) = 306 (M$^+$, 13), 139 (100), 111 (33), 75 (12).

1,4-Bis(4-chlorophenyl)butane-1,4-dione (2c)

Yield: 97%; colorless crystals; mp 149–152 °C ($CHCl_3$) (Lit.[25] mp 148–149 °C).

IR (KBr): 3070, 3060, 3037, 2998, 2952, 1693, 1587, 1508, 1199, 1091, 991, 811, 725 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.96 and 7.46 (AA′BB′ system, 8 H_{arom}), 3.41 (s, 4 H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.27, 141.67, 137.03, 131.52, 130.94, 34.48.

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MS: *m*/*z* = 306 (M$^+$, 10), 139 (100), 111 (33), 75 (23).

1,4-Bis(2-bromophenyl)butane-1,4-dione (2d)

Yield: 29%; colorless crystals: mp 132 °C (benzene).

IR (film): 3064, 2958, 2925, 2869, 1698, 1587, 1465, 1427, 1355, 1282, 1241, 1025, 755, 593 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 7.62 (m, 2 H), 7.44 (m, 2 H), 7.32 (m, 4 H), 3.34 (s, 4 H, CH$_2$).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 199.05, 135.68, 132.64, 130.90, 130.42, 121.88, 38.46.

Anal. Calcd for C$_{16}$H$_{12}$Br$_2$O$_2$: C, 48.52; H, 3.05. Found: C, 48.49; H, 3.04.

1,4-Bis(3-bromophenyl)butane-1,4-dione (2e)

Yield: 51%; colorless crystals; mp 168 °C (CHCl$_3$–hexane) (Lit.[26] mp 170–172 °C).

IR (KBr): 3081, 3064, 3027, 2962, 2927, 1691, 1675, 1567, 1452, 1288, 1099, 800, 781, 674 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 8.17 (m, 2 H), 7.96 (m, 2 H), 7.72 (m, 2 H), 7.34 (m, 2 H), 3.42 (s, 4 H, CH$_2$).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 198.80, 138.50, 132.34, 130.00, 129.21, 128.86, 124.92, 34.34.

MS: *m*/*z* = 396 (M$^+$, 12), 183 (100), 155 (43), 76 (22).

1,4-Bis(4-bromophenyl)butane-1,4-dione (2f)

Yield: 96%; colorless crystals; mp 182 °C (CHCl$_3$–hexane) (Lit.[27] mp 182–183 °C).

IR (film): 3091, 3062, 3035, 2954, 2896, 1671, 1583, 1392, 1324, 1189, 1072, 1000, 848, 784, 761 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 7.88 and 7.64 (AA′BB′ system, 8 H$_{\text{arom}}$), 3.41 (s, 4 H, CH$_2$).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 199.43, 137.46, 133.94, 131.61, 130.37, 34.46

MS: *m*/z (%) = 396 (M$^+$, 8), 183 (100), 155 (24), 76 (15).

1,4-Bis(2-methoxyphenyl)butane-1,4-dione (2g)

Yield: 26%; colorless crystals; mp 98–102 °C (benzene) (Lit.[28] mp 102–104 °C).

IR (film): 3072, 3002, 2960, 2937, 2046, 1930, 1673, 1463, 1292, 1180, 1024, 788 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 7.41 (m, 2 H), 7.21 (m, 2 H), 6.99 (m, 4 H), 3.90 (s, 6 H, OCH$_3$), 3.77 (s, 4 H, CH$_2$).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 199.14, 160.94, 135.75, 132.36, 123.24. 122.54, 113.59, 57.50, 33.92.

Anal. Calcd for C$_{18}$H$_{18}$O$_4$: C, 72.47; H, 6.08. Found: C, 72.43; H, 6.11.

1,4-Bis(3-methoxyphenyl)butane-1,4-dione (2h)

Yield: 60%; colorless crystals; mp 128 °C (CHCl$_3$–hexane).

IR (KBr): 3062, 3027, 2960, 2929, 2871, 1963, 1911, 1816, 1677, 1596, 1448, 1272, 1211, 1072, 1000, 919, 875, 755, 696 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 7.68 (m, 2 H), 7.56 (m, 2 H), 7.40 (m, 2 H), 7.16 (m, 2 H), 3.85 (s, 6 H, OCH$_3$), 3.42 (s, 4 H, CH$_2$).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 200.44, 161.86, 140.19, 131.57, 122.88, 121.68, 114.36, 57.45, 34.78.

MS: *m*/*z* (%) = 298 (M$^+$, 5), 105 (100), 77 (31).

1,4-Bis(4-methoxyphenyl)butane-1,4-dione (2i)

Yield: 32%; colorless crystals; mp 155–159 °C (benzene) (Lit.[25] mp 153–155 °C).

IR (film): 3068, 3006, 2962, 2937, 2840, 1679, 1598, 1509, 1259, 1172, 1031, 788 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 7.89 and 6.89 (AA′XX′ system, 8 H$_{\text{arom}}$), 3.91 (s, 4 H, CH$_2$), 3.82 (s, 6 H, OCH$_3$).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 198.84, 165.48, 132.58, 132.35, 115.66, 57.47, 34.28.

Anal. Calcd for C$_{18}$H$_{18}$O$_4$: C, 72.47; H, 6.08. Found: C, 72.44; H, 6.05.

2,3-Dimethyl-1,4-diphenylbutane-1,4-dione (2j)

Yield: 79%; colorless crystals; mp 79 °C (benzene) (Lit.[29] 85–86 °C).

IR (KBr): 3068, 2958, 2925, 2856, 1702, 1589, 1428, 1220, 1027, 987, 796, 698 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 7.99 (m, 2 H), 7.72 (m, 2 H), 7.48 (m, 6 H), 3.91 (m, 2 H, CH), 1.25 (d, 6 H, CH$_3$).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 203.02, 149.26, 131.69, 130.55, 127.29, 33.85, 12.91.

Anal. Calcd for C$_{18}$H$_{18}$O$_2$: C, 81.17; H, 6.81. Found: C, 81.15; H, 6.84.

1,2,3,4-Tetraphenylbutane-1,4-dione (2k)

Yield: 87% from **1k**; 98% from **1l**; colorless crystals; mp 157–160 °C (Lit.[30] mp 158–162 °C).

IR (KBr): 3085, 3064, 3031, 2962, 2927, 1695, 1598, 1448, 1272, 1012, 871, 698 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 8.07 (m, 4 H), 7.53 (m, 4 H), 7.30 (m, 12 H), 4.32 (s, 2 H, CH$_2$).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 196.62, 138.71, 136.64, 135.17, 132.95, 132.45, 131.93, 131.52, 131.08, 130.96, 130.89, 130.66, 130.43, 129.38, 129.23, 128.92, 127.91, 47.54.

MS: *m*/*z* (%) = 390 (M$^+$,5), 372 (100), 267 (34), 105 (11), 77 (8).

3,4-Diacetylhexane-2,5-dione (2l)

Yield: 68%; colorless crystals; mp 188 °C (Lit.[31] mp 192–193 °C).

IR (KBr): 3064, 3031, 2962, 2931, 1685, 1598, 1448, 1319, 1288, 1209, 1176, 698 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 5.48 (s, 2 H, CH), 2.11 (s, 12 H, CH$_3$).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 195.88, 62.08, 19.42.

MS: *m*/*z* (%) = 198 (M$^+$, 7), 182 (34), 91 (100), 65 (12).

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