# A New Simple Synthesis of Aryl-Substituted 1,4-Diketones

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*Received 17 July 1995*

1,4-Diketones have been prepared by aldol condensation of methyl ketones with α-bromo ketones in the presence of *tert*-butoxymagnesium or diethylamido magnesium bromide and subsequent rearrangement of the formed 4-bromo-3-hydroxy ketones under the action of triethylamine.

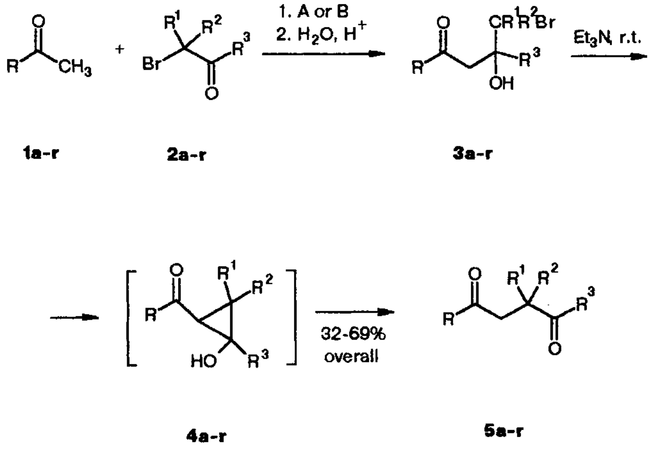
1,4-Diketones are widely used in the synthesis of five-membered carbocyclic[1] and heterocyclic[2] compounds, including the preparation of derivatives of terthiophene and other conjugated, five-membered heterocycles, which are being intensively investigated at present as monomers for electroconductive polymers.[3]

A number of methods for the synthesis of 1,4-diketones are known,[4-7] and among them, reactions with the participation of α-halo ketones[8-12] as readily available substrates seem to be the most promising. Thus, the alkylations of stabilized alkaline metal enolates,[8,12] tin enolates,[9,10] and enamines[11,12] by α-halo ketones have been described. However, these methods have essential shortcomings, mainly due to the limited choice of starting nucleophiles.

In our present research, we have elaborated a simple method for the synthesis of aryl-substituted 1,4-diketones using readily available methyl ketones and α-bromo ketones. The method is based on the application of magnesium reagents in the cross-aldol condensation of methyl ketones **1a–r** with α-bromo ketones **2a–r**, and subsequent rearrangement of the formed 4-bromo-3-hydroxy ketones **3a–r**. The use of these condensation agents completely prevents the epoxide ring closure[13] in the generated aldols with formation of Darzen's reaction products[14] or β,γ-epoxy ketones.[9,15] It is noteworthy also, that alkyl methyl ketones **1e, q** under the action of these bases selectively react at the methyl group.

Condensations of methyl ketones **1a–e** with α-bromomethyl ketones **2a–e** were carried out in the presence of *tert*-butoxymagnesium bromide etherate in benzene at room temperature (method A) to give compounds **3a–e**, and of them **3a** has been isolated. The structures of the other products **3b–e** were confirmed by comparison of typical groups of signals in $^1$H NMR spectra of the reaction mixtures with those for compound **3a**. While exploring the reaction course by $^1$H NMR and TLC, we found that products of the self-condensations of the α-bromo ketone **2a–e** are initially formed.[16] Products **3a–e** of the cross-aldol condensation are formed under thermodynamic control and the equilibrium is achieved within 2–3 days.

α-Bromo ketones **2f–r** containing secondary or tertiary α-carbon atoms or electron-donor substituents in the aromatic ring did not give satisfactory results when *tert*-butoxymagnesium bromide was applied as the condensation agent. We assume, that the latter promotes carbon–bromine bond heterolysis in the generated 4-bromo-3-hydroxy ketones **3f–r**, followed by sigmatropic rearrangements to form 1,3-diketones as byproducts.[17] At the same time, the condensation can be successfully performed using diethylamidomagnesium bromide, which has less pronounced Lewis acidity (method B). The application of this reagent with an additional equivalent of diethylamine gave the best results in the reactions with α-bromo ketones **2k, m, h** (Table 1). In these cases, mixtures of 4-bromo-3-hydroxy ketone **3f–r** and 1,4-diketone **5f–r** are formed as a result of the condensation.



A. t-BuOMgBr·Et$_2$O, benzene, r.t., 48h
B. Et$_2$NMgBr·Et$_2$O, toluene, 0-20$^\circ$C, 3h

**Scheme**

The 4-bromo-3-hydroxy ketones **3a–r** were transformed into 1,4-diketones without isolation. The reaction occurs smoothly on treatment with triethylamine at room temperature.[15] We assume that this conversion proceeds via 1,3-dehydrobromination and cleavage of the cyclopropane ring in the 3-hydroxycyclopropyl ketones **4a–r** formed. The latter compounds could not be isolated because of their instability, which is apparently caused by the presence of electron-donor and electron-acceptor substituents in the vicinal position of three-membered carbon ring.[18]

In conclusion, the method described allows the preparation of aryl-substituted 1,4-diketones in acceptable yields using readily available starting materials. This procedure appears to be most effective for the synthesis of branched 1,4-diketones.[3]

$^1$H NMR spectra were recorded on a "Tesla-BS467A" (60 MHz) spectrometer. IR spectra were obtained on a "Specord IR-75" spectrophotometer. Methyl ketones **1a–r** and α-bromo ketones **2a, f, k**

**Table 1.** 1,4-Diketones **5a–r** Prepared.

| Product[a] | R | R$^1$ | R$^2$ | R$^3$ | Method | Yield[b] | mp (°C) or $n_d^{20}$ | Solvent for crystallisation | $^1$H NMR (HMDS) $\delta$, $J$ (Hz) |
|---|---|---|---|---|---|---|---|---|---|
| **5a** | Ph | H | H | Ph | A | 58 | 144–145[c] | $Me_2CO$ | (acetone-$d_6$), 3.38 (s, 4 H), 7.3–7.6 (m, 6 H), 7.8–8.1 (m, 4 H) |
| **5b** | 2-thienyl | H | H | Ph | A | 63 | 119–120 | *i*-PrOH | ($CDCl_3$) 3.28 (s, 4 H), 6.9–8.1 (m, 8 H) |
| **5c** | 4-$MeOC_6H_4$ | H | H | Ph | A | 61 | 106[d] | EtOH | (acetone-$d_6$) 3.33 (s, 4 H), 3.80 (s, 3 H), 6.93 (d, 2 H, $J = 9$), 7.4–7.6 (m, 3 H), 7.8–8.1 (m, 4 H) |
| **5d** | Ph | H | H | 4-$MeO_2CC_6H_4$ | A | 54 | 144–145 | $Me_2CO$ | (acetone-$d_6$) 3.40 (s, 4 H), 3.87 (s, 3 H), 7.3–7.6 (m, 3 H), 7.8–8.0 (m, 2 H), 8.08 (s, 4 H) |
| **5e** | Et | H | H | Ph | A | 50 | 1.5258 | – | ($CCl_4$) 0.93 (t, 3 H, $J = 8$), 2.33 (q, 2 H, $J = 8$), 2.4–2.7 (m, 2 H), 2.8–3.2 (m, 2 H), 7.0–7.5 (m, 3 H), 7.7–7.9 (m, 2 H) |
| **5f** | Ph | H | Me | Ph | B | 53 | 104–105[e] | *i*-PrOH | (acetone-$d_6$), 1.15 (d, 3 H, $J = 7$), ABX $\delta_A = 3.03$, $\delta_B = 3.75$ $\delta_X = 4.05$, (3 H, $J_{AX} = 9$, $J_{AB} = 18$), 7.2–7.6 (m, 6 H), 7.8–8.1 (m, 4 H) |
| **5g** | Ph | H | Me | 2-thienyl | B | 50 | 85 | $CCl_4$ | ($CCl_4$) 1.13 (d, 3 H, $J = 6$), ABX $\delta_A = 2.80$, $\delta_B = 3.50$, $\delta_X = 3.77$ (3 H, $J_{AX} = 5$, $J_{BX} = 8$, $J_{AB} = 17$), 6.97 (dd, 1 H, $J = 3$, $J = 4$), 7.2–7.9 (m, 7 H) |
| **5h** | Ph | H | Me | 4-$MeOC_6H_4$ | B[f] | 54 | 88–89 | *i*-PrOH | ($CCl_4$) 1.02 (d, 3 H, $J = 7$), ABX $\delta_A = 2.73$, $\delta_B = 3.50$, $\delta_X = 3.83$ (3 H, $J_{AX} = 5$, $J_{BX} = 7$, $J_{AB} = 17$), 3.67 (s, 3 H), 6.73 (d, 2 H, $J = 9$), 7.1–7.4 (m, 3 H), 7.7–8.0 (m, 4 H) |
| **5i** | Ph | H | Me | Et | B | 44 | 1.5216 | – | ($CCl_4$) 0.90 (t, 3 H, $J = 7$), 0.96 (d, 3 H, $J = 7$), 2.42 (q, 2 H, $J = 7$), 2.7–3.6 (m, 3 H), 7.1–7.4 (m, 3 H), 7.6–7.9 (m, 2 H) |
| **5j** | Ph | H | *i*-Pr | Ph | B | 62 | 45–46 | pentane/ $Et_2O$ (2 : 1) | ($CCl_4$) 0.78 (dd, 6 H, $J = 7$, $J = 8$), 1.6–2.2 (m, 1 H), ABX $\delta_A = 2.77$, $\delta_B = 3.60$, $\delta_X = 3.87$ (3 H, $J_{AX} = 2$, $J_{BX} = 8$, $J_{AB} = 17$), 7.1–7.5 (m, 6 H), 7.7–8.0 (m, 4 H) |
| **5k** | Ph | Me | Me | Ph | B[f] | 63 | 57–58 | MeOH | ($CCl_4$) 1.23 (s, 6 H), 3.27 (s, 2 H), 7.1–7.9 (m, 10 H) |
| **5l** | 2-thienyl | H | Me | 2-thienyl | B | 41 | 72 | MeOH | ($CCl_4$) 1.70 (d, 3 H, $J = 7$), ABX $\delta_A = 2.82$, $\delta_B = 3.48$, $\delta_X = 3.80$ (3 H, $J_{AX} = 5$, $J_{BX} = 8$, $J_{AB} = 17$), 7.0–7.3 (m, 2 H), 7.6–8.0 (m, 4 H) |
| **5m** | 2-thienyl | H | Ph | 2-thienyl | B[f] | 46 | 151–152 | $Me_2CO$ | ($CDCl_3$) 3.05 (dd, 1 H, $J = 4$, $J = 18$), 3.93 (dd, 1 H, $J = 10$, $J = 18$), 5.00 (dd, 1 H, $J = 4$, $J = 10$), 6.7–7.7 (m, 11 H) |
| **5n** | 2-thienyl | H | *n*-$C_{16}H_{33}$ | 2-thienyl | B | 69 | 40–41 | pentane | ($CCl_4$) 0.7–1.8 (m, 33 H), ABX $\delta_A = 2.83$, $\delta_B = 3.45$, $\delta_X = 3.73$ (3 H, $J_{AX} = 5$, $J_{BX} = 8$, $J_{AB} = 17$), 7.0–7.2 (m, 2 H), 7.5–7.9 (m, 4 H) |
| **5o** | 2-thienyl | H | $(CH_2)_7CO_2Et$ | 2-thienyl | B | 63 | 1.5526 | – | ($CCl_4$) 0.8–1.6 (m, 15 H), 1.9–2.2 (m, 2 H), ABX $\delta_A = 2.80$, $\delta_B = 3.42$, $\delta_X = 3.73$ (3 H, $J_{AX} = 5$, $J_{BX} = 8$,. $J_{AB} = 17$), 3.96 (q, 2 H, $J = 7$), 6.9–7.1 (m, 2 H), 7.4–7.9 (m, 4 H) |
| **5p** | 2-thienyl | H | Me | Ph | B | 40 | 84 | *i*-PrOH | ($CCl_4$) 1.03 (d, 3 H, $J = 7$), 2.66 (dd, 1 H, $J = 5$, $J = 17$), 3.33 (dd, 1 H, $J = 7$, $J = 17$), 3.90 (sextet, 1 H, $J = 7$), 6.86 (dd, 1 H, $J = 4$, $J = 5$), 7.1–7.9 (m, 7 H) |
| **5q** | *n*-$C_6H_{13}$ | H | Me | 2-thienyl | B[f] | 32 | 1.5225 | – | ($CCl_4$) 0.6–1.6 (m, 14 H), 2.0–2.5 (m, 3 H), 2.87 (dd, 1 H, $J = 8$, $J = 18$), 3.53 (sextet, 1 H, $J = 7$), 6.97 (dd, 1 H, $J = 4$, $J = 5$), 7.53 (ddd, 2 H, $J = 1.5$, $J = 4$, $J = 8$) |
| **5r** | 4-$BrC_6H_4$ | H | Me | 2-thienyl | B | 52 | 92–93 | *i*-PrOH | ($CCl_4$) 1.15 (d, 3 H, $J = 7$), ABX $\delta_A = 2.73$, $\delta_B = 3.47$, $\delta_X = 3.73$ (3 H, $J_{AX} = 4$, $J_{BX} = 8$, $J_{AB} = 17$), 6.97 (dd, 1 H, $J = 4$, $J = 5$), 7.3–7.8 (m, 6 H) |

**Table 1.** (continued)

[a] For new compounds satisfactory microanalyses were obtained: C ± 0.28, H ± 0.25.
[b] Yield of isolated product based on **2**.
[c] Lit.[5] 143–144 °C.
[d] Lit.[6] mp 106 °C.
[e] Lit.[7] mp 105 °C.
[f] The condensation was carried out in the presence of $Et_2NH$ (12 mmol) for 3 h at 0 °C.

were commercially available. Other α-bromo ketones were synthesized by the bromination of corresponding ketones with dioxane dibromide.[19] The starting 2-thienyl ketones were obtained by acylation of thiophene with the corresponding acyl chlorides.[20] The solvents *t*-BuOH and $Et_2NH$ were dried by distillation from Na before use.

**4-Bromo-1,3-diphenyl-3-hydroxybutan-1-one (3a):**
In a one-neck, round-bottom, 30-mL flask fitted with a magnetic stirrer and reflux condenser were placed Mg (0.36 g, 15 mmol), $Et_2O$ (2.2 mL), and EtBr (0.2 mL). After the reaction had started, a solution of EtBr (1.1 mL, 15 mmol) in benzene (20 mL) was added slowly dropwise through the reflux condenser. After the reaction was complete, the solution was cooled to 0 °C, and *t*-BuOH (1.4 mL, 15 mmol) was carefully added. The cooling bath was removed, and acetophenone (**1a**; 1.75 mL, 15 mmol) and α-bromoacetophenone (**2a**; 1.99 g, 10 mmol) were added. The mixture was allowed to stand at r.t. for 2 days with occasional stirring; it was then cooled and worked up with cold 5% aq $H_2SO_4$. The organic phase was washed twice with 5% aq NaCl, dried ($Na_2SO_4$), and concentrated under vacuum at a temperature not exceeding 35–40 °C. The residue was chromatographed on silica gel with benzene/hexane (4 : 1) eluent to afford **3a**. Yield: 58%; mp 56–57 °C (from $Et_2O$–pentane), lit.[15] mp 56–57 °C. IR and $^1H$NMR data were in agreement with the published data.[10,15]

**1,4-Diketones 5a–r; General Procedure:**
Method A: 4-Bromo-3-hydroxy ketones **3a–e** were prepared as above from methyl ketones **1a–e** (15 mmol) and α-bromo ketones **2a–e** (10 mmol). After treatment with 5% aq $H_2SO_4$ (20 mL), the organic layer was separated, dried ($Na_2SO_4$), concentrated under vacuum (35–40 °C), and then dioxane (10 mL) and $Et_3N$ (1.45 mL, 10 mmol) were added to the residue. The mixture was allowed to stand for 20 h at r.t., then concentrated under vacuum, and the residue was mixed with MeOH (10 mL). 1,4-Diketones **5a–d** were filtered, washed with MeOH, and dried. 1,4-Diketone **5e** was obtained by chromatography of the residue on alumina with $Et_2O$/hexane (1 : 2) eluent.

Method B: To a solution of EtMgBr etherate in toluene, prepared as described above from Mg (0.29 g, 12 mmol), EtBr (1.05 mL, 13 mmol), $Et_2O$ (1.8 mL), and toluene (30 mL), was added $Et_2NH$ (1.24 mL, 12 mmol). The solution was stirred for 15 min and cooled to 0 °C. A mixture of the methyl ketone **1f–r** (12 mmol) and the α-bromo ketone **2f–r** (10 mmol) without the solvent or in a minimum quantity of toluene was quickly added. If a viscous residue appeared the stirring was stopped. The mixture was kept for 3 h at 0 °C or, in the cases of the preparations of compounds **5g, l, o, p, r** for 1 h at 0 °C and 2 h at r.t. After treatment with 5% aq $H_2SO_4$ (20 mL), the organic layer was separated and $Et_3N$ (1.4 mL, 10 mmol) was added. The mixture was allowed to stand overnight, then washed with $H_2O$, dried ($Na_2SO_4$), and concentrated under vacuum. 1,4-Diketones **5f–r** were isolated by crystallisation [mainly from $Et_2O$ (10 mL)] or by column chromatography on alumina with benzene–hexane as eluent.

*We are indebted to International Science Foundation (ISF) for financial support.*

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