One Step Preparation of 1,4-Diketones from Methyl Ketones and α-Bromomethyl Ketones in the Presence of $ZnCl_2$·*t*-BuOH·Et_2NR as a Condensation Agent

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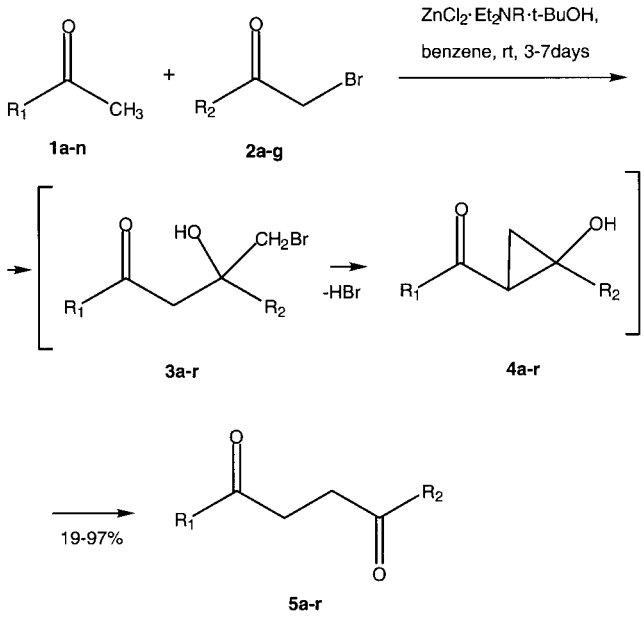
Abstract: 1,4-Diketones have been prepared in one step from methyl ketones and α-bromomethyl ketones under the action of $ZnCl_2$·*t*-BuOH·Et_2NR as a condensation agent with moderate to high yields. The mechanistic pathway of the reaction is proposed to go through aldol condensation of ketones followed by 1,3-dehydrobromination of aldol products and cleavage of activated cyclopropyl intermediates.

Key words: α-bromo ketones, 1,4-diketones, aldol condensation, 3-bromo-2-hydroxy ketones, activated cyclopropanes

1,4-Diketones are useful synthetic intermediates for the preparation of five-membered carbocyclic and heterocyclic compounds.[1] Among the most convenient methods for the synthesis of asymmetrical 1,4-diketones,[2-15] the Michael−Stetter addition of aldehydes to α,β-unsaturated ketones,[6-10] as well as alkylation of stabilized alkaline metal enolates,[10-13] enamines,[13,14] and tin enolates[15] by α-halocarbonyl compounds should be mentioned. However, to our knowledge, the Michael−Stetter method does not give satisfactory results with electron-poor aromatic substrates,[10] and the last three methods are restricted mainly by aromatic or symmetrical aliphatic starting nucleophiles, which should be prepared from the corresponding carbonyl compounds.

Recently, we have reported a new simple and regioselective method for the preparation of 1,4-diketones directly from methyl ketones and α-bromo ketones.[16,17] This method is based on the thermodynamically controlled cross aldol condensation of methyl ketones with α-bromo ketones followed by 1,3-dehydrobromination of the aldol products and cleavage of the corresponding intermediate activated cyclopropyl derivatives to 1,4-diketones. Using this approach, we have developed two main preparative procedures. The first is based on the application of two separate stages: aldol condensation of methyl ketones with α-bromo ketones in the presence of magnesium bases, and subsequent conversion of the aldol products into 1,4-diketones by treatment with tertiary amine.[16] In the second procedure, we have succeeded in combining these both stages into one using titanium isopropoxide as the condensation agent.[17]

In this paper, we propose another simple one step procedure for the preparation of 1,4-diketones **5a−r** from methyl ketones **1a−n** and α-bromo ketones **2a−g**, which gives better results for the synthesis of products with strong



Scheme

1	R_1[a]	**2**	R_2[a]
a	Me	**a**	Me
b	Et	**b**	Ph
c	C_6H_{13}	**c**	4-BrC_6H_4
d	Ph	**d**	3-$O_2NC_6H_4$
e	2-naphthyl	**e**	4-$O_2NC_6H_4$
f	PhCH=CH	**f**	2-(5-bromothienyl)
g	4-$MeOC_6H_4$	**g**	2-(5-cyanothienyl)
h	4-$MeO_2CC_6H_4$		
i	4-$CH_3COC_6H_4$		
j	4-$O_2NC_6H_4$		
k	3-$O_2NC_6H_4$		
l	4-BrC_6H_4		
m	2-thienyl		
n	2-(5-bromothienyl)		

[a] Compounds **3**–**5**: R_1, R_2, see Table 1.

Table 1 1,4-Diketones **5a–s** Prepared

Product[a]	R_1	R_2	Time (days)	Amine	Yield[d] (%)	Mp (°C) (Solvent)
5a	Me	4-BrC_6H_4	3	Et_2NH	64	84-85[f] *i*-PrOH
5b	Et	4-BrC_6H_4	3	Et_2NH	19	53-54 Et_2O
5c	*n*-C_6H_{13}	Me	3	Et_2NH	25	oil[g]
5d	Ph	Me	3	Et_3N	44	28-29[h] *i*-PrOH
5e	Ph	Ph	3	Et_2NH	64	144-145[i] EtOAc
5f	Ph	4-BrC_6H_4	3	Et_2NH	75	116-117[j] *i*-PrOH
5g	PhCH=CH	Ph	3	Et_2NH	72	116-117[k] EtOAc
5h	4-$MeOC_6H_4$	Ph	7	Et_3N	37	105-106[l] *i*-PrOH
5i	4-$MeO_2CC_6H_4$	Ph	7	Et_3N	97 86[e]	144-145 EtOAc
5j[b]	4-$MeCOC_6H_4$	Ph	3	Et_2NH	84[e]	138-139 EtOAc
5k[c]	4-$PhCOCH_2CH_2COC_6H_4$	Ph	3	Et_2NH	71	198-200 *n*-BuOH
5l	3-$O_2NC_6H_4$	Ph	7	Et_3N	75	92 MeOH
5m	4-$O_2NC_6H_4$	Ph	3	Et_3N	66	140-142 *i*-PrOH
5n	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	3	Et_2NH	95	195-196 $CHCl_3$
5o	4-BrC_6H_4	3-$O_2NC_6H_4$	7	Et_3N	64	163-164 EtOAc
5p	2-naphthyl	4-BrC_6H_4	3	Et_2NH	71[e]	153 EtOAc
5q	2-thienyl	2-(5-bromothienyl)	3	Et_2NH	75	114 MeOH
5r	2-(5-bromothienyl)	2-(5-cyanothienyl)	3	Et_2NH	80	141-142 EtOAc

[a] For new compounds satisfactory microanalyses were obtained: C ± 0.33; H ± 0.15.
[b] Ratio of starting compounds was: **1i**/**2b**/$ZnCl_2$ = 3/1/2.
[c] Ratio of starting compounds was: **1i**/**2b**/$ZnCl_2$ = 1/3/2.
[d] Yield of isolated product based on **2**.
[e] Yield of product after isolation and recrystallization.
[f] Lit.[3] mp: 86°C.
[g] Lit.[4] mp: 33-34°C.
[h] Lit.[6] mp: 28-29°C.
[i] Lit.[5] mp: 143-144°C.
[j] Lit.[12] mp: 112-113°C.
[k] Lit.[8] mp 115°C.
[l] Lit.[9] mp 106°C.

Table 2 ^{1}H NMR Spectra of New 1,4-Diketones **(5b**, **i–r)**.

Product	^{1}H NMR[a] δ, *J* (Hz)
5b	($CDCl_3$): 1.08 (t, 3 H, *J* = 8), 2.54 (q, 2 H, *J* = 8), 2.84 (t, 2 H, *J* = 7), 3.14 (t, 2 H, *J* = 7), 7.08 (d, 2 H, *J* = 4), 7.50 (d, 2 H, *J* = 4)
5i[b]	(acetone-d_6): 3.40 (s, 4 H), 3.90 (s, 3 H), 7.30–7.63 (m, 3 H), 7.77–8.20 (m, 6 H)
5j	($CDCl_3$): 2.66 (s, 3 H), 3.48 (s, 4 H), 7.44–7.68 (m, 3 H), 7.96–8.24 (m, 6 H)
5k	($CDCl_3$): 3.50 (s, 8 H), 7.44–7.68 (m, 6 H), 7.98–8.22 (m, 8 H)
5l[b]	($CDCl_3$): 3.33 (s, 4 H), 7.03–7.36 (m, 4 H), 7.67–7.97 (m, 2 H), 8.00–8.33 (m, 2 H), 8.50–8.77 (m, 1 H)
5m[b]	(CCl_4): 3.30 (s, 4 H), 7.27–7.60 (m, 3 H), 7.80–8.30 (m, 6 H)
5n	($CDCl_3$): 3.54 (s, 4 H), 8.20 (d, 4 H, *J* = 9), 8.38 (d, 4 H, *J* = 9)
5o[b]	($CDCl_3$): 3.33 (s, 4 H), 7.27–7.97 (m, 5 H), 8.03–8.50 (m, 2 H), 8.60–8.83 (m, 1 H)
5p	($CDCl_3$): 3.46 (t, 2 H, *J* = 6), 3.60 (t, 2 H, *J* = 6), 7.46–7.72 (m, 4 H), 7.80–8.20 (m, 6 H), 8.58 (s, 1 H)
5q	($CDCl_3$): 3.36 (q, 4 H, *J* = 5), 7.06–7.20 (m, 2 H), 7.56 (d, 1 H, *J* = 4), 7.66 (dd, 1 H, *J* = 5, 1.5), 7.80 (dd, 1 H, *J* = 5, 1.5)
5r	($CDCl_3$): 3.36 (s, 4 H), 7.14 (d, 1 H, *J* = 4), 7.56 (d, 1 H, *J* = 4), 7.66 (d, 1 H, *J* = 4), 7.76 (d, 1 H, *J* = 4)

[a]Spectra were recorded on a Brucker AC200 (200 MHz) spectrometer.
[b]Spectra were recorded on a Tesla BS-467A (60 MHz) spectrometer.

electron-withdrawing functional groups (**5i–o, r**) in comparison with Michael–Stetter[10] or titanium isopropoxide[17] methods. The new procedure is based on the application of anhydrous zinc chloride–amine–*tert*-butyl alcohol complex as the condensation agent. This reagent was prepared by dissolving 25% excess of freshly dried anhydrous zinc chloride in benzene in the presence of equimolecular amounts of di- or triethylamine and *tert*-butyl alcohol. The most reactive complex was found to be prepared with diethylamine, but in the cases of very reactive starting bromo ketones, such as bromoacetone **2a** or 3′-nitro-2-bromoacetophenone **2d**, triethylamine gave better results (Scheme, Table 1).

The reactions of methyl ketones **1a–n** with α-bromo ketones **2a–g** in the presence of zinc reagent were generally complete at room temperature in 24 hours, but in order to achieve the highest conversion the mixture was kept for 3–7 days. Methyl ketone reacts only as a nucleophile and bromo ketone as an electrophile and neither the reversal of the roles of reactants nor self-condensation of components[16] (except bromoacetone **2a**) has been observed.

Very mild and almost neutral reaction conditions allowed us to obtain good results with starting compounds containing different functional groups, including strongly electron-withdrawing, such as nitro **1j**, **k**; **2d**, **e**, alkoxycarbonyl **1h**, cyano **2g**, acyl **1i**, and activated electrophilic double bond **1f**. 1,4-Diacetylbenzene **1i** was condensed by one **5j** as well as by both **5k** acetyl groups.

Some limitations of this procedure should also be mentioned. Moderate yields were obtained with electron-rich aromatic ketone **1g** and akyl methyl ketones **1b**, **c** (except acetone **1a**), apparently due to their low reactivity. Attempts to increase a low conversion ratio of starting ketones in these cases by prolonged reaction time at room temperature or heating failed because of the side-reaction of amination of the bromo ketone. Moderate yields in the case of bromoacetone **2a** depend apparently upon fast self-condensation due to the presence of methyl ketone and bromomethyl ketone fragments in the same molecule. Contrary to the two step procedure,[16] alkyl bromomethyl ketones (except bromoacetone **2a**), and aromatic bromo ketones with secondary or tertiary α-carbon atoms from the bromine moiety were unreactive under the present reaction conditions.

We believe that the reaction pathway through the aldol condensation of methyl ketones **1a–n** and α-bromo ketones **1a–g** with formation of 3-bromo-2-hydroxyketones **3a–r** as intermediates and their subsequent rearrangement via activated cyclopropyl ketones **4a–r** to 1,4-diketones **5a–r** is preferable, in this case, rather than possible direct alkylation of the enolate of methylketone by bromo ketone from the bromine moiety.[10-12] Formation of small amounts of 3-bromo-2-hydroxyketones **3a–r** was observed by TLC after the start of the reaction, however, the presence of intermediate 2-hydroxycyclopropylketones **4a–r** was not detected. We assume that 2-hydroxycyclopropylketones **4a–r** are very unstable due to the presence of strong electron donating and electron withdrawing groups in vicinal positions on the cyclopropane ring.[18] Proposed intermediate **3e,** prepared by another method (see experimental), smoothly afforded 1,4-diketone **5e** in good yield by treatment with the zinc condensation agent under standard reaction conditions, and this is in agreement with the described mechanism.

In conclusion, the method described can be useful for preparation of functionalized asymmetrical 1,4-diketones in mild conditions. Best results are obtained with starting

compounds containing electron withdrawing functional groups.

^{1}H NMR spectra were recorded on a Tesla-BS 467A (60 MHz) and Brucker AC-200 (200 MHz) spectrometers (Table 2). Methyl ketones **1a−m**, and α−bromo ketones **2b−e** were commercially available. 2-Acetyl-5-bromothiophene (**1n**) was prepared by bromination of 2-acetylthiophene with NBS.[19] α-Bromo ketones **2a**, **f−g** were synthesized by bromination of the corresponding ketones with dioxane dibromide.[20] 5-Cyano-2-acetylthiophene was synthesized by reaction of 5-iodo-2-acetylthiophene with copper (I) cyanide.[21] The solvents, *t*-BuOH and Et_2NH, Et_3N were dried by distillation from Na before use.

1, 4-Diketones 5a−r; General Procedure

Commercial anhyd $ZnCl_2$ (2.72 g, 20 mmol) was placed into a one-neck, 25-mL round-bottom flask and dried by melting under vacuum (1 torr) at 250−350 °C for 15 min. After cooling under vacuum to r.t., benzene (10 mL), di- or triethylamine (Table 1) (15 mmol), and *t*-BuOH (1.4 mL, 15 mmol) were successively added. The mixture was stirred until zinc chloride was fully dissolved (approx 2 h), and methyl ketone (**1a−n**) (15 mmol) and α-bromo ketone (**2a−g**) (10 mmol) were successively dded. The mixture was stirred for 1 h, allowed to stand for 3−7 days at r.t., quenched with 5% aq H_2SO_4 and filtered (in the cases of precipitation of crystalline diketones). Crystalline products were washed successively with benzene, H_2O and MeOH, and recrystallized (Table 1). Quenched mixture or combined filtrates were placed in a separatory funnel, the organic layer was separated, washed twice with 5% aq NaCl and dried (Na_2SO_4). The solvent was evaporated under vacuum, and the residue was crystallized by mixing with MeOH (10 mL) to afford an additional amount of diketone (**5e−r**). Compounds **5a−d** were isolated by column chromatography (silica gel) using benzene or benzene-hexane mixtures as the eluent. ^{1}H NMR data are listed in Table 2.

4-Bromo-3-hydroxy-1,3-diphenylbutan-1-one (3e)

α-Bromoacetophenone (**2b**) (1.99 g, 10 mmol) was added to a solution of *t*-BuOMgBr·Et_2O[16] (11 mmol) in benzene (5 mL). The mixture was stirred for 24 h, quenched with cold 5% aq H_2SO_4, washed twice with 5% aq NaCl, and dried (Na_2SO_4). The solvent was evaporated under vacuum, and the residue was crystallized from CCl_4/hexane (1:1) (10 mL) to afford *erythro*-2,4-dibromo-3-hydroxy-1,3-diphenylbutan-1-one.[16]

Yield: 1.79 g (90%); mp: 99−100 °C (dec).

^{1}H NMR (CCl_4): δ = 3.40 (d, 1H, *J* = 10 Hz), 3.83 (d, 1H, *J* = 10 Hz), 5.00 (s, 1H), 5.93 (s, 1H), 6.90−7.50 (m, 8H), 7.70−7.90 (m, 2H).

Zinc powder (0.98 g, 15 mmol) was added in small portions with stirring and cooling (0 °C) to the mixture of *erythro*-2,4-dibromo-3-hydroxy-1,3-diphenylbutan-1-one (3.98 g, 10 mmol) and HOAc (20 mL). After the zinc dissolved (5−10 min) the mixture was poured into H_2O (200 mL), and extracted with benzene (40 mL). The organic layer was separated, successively washed with 5% aq Na_2CO_3, 5% aq NaCl, and dried (Na_2SO_4). Benzene was evaporated under vacuum at 35 °C to afford 4-bromo-3-hydroxy-1,3-diphenylbutan-1-one[16] (**3e**). Yield: 2.56 g (80%).

1,4-Diphenylbutane-1,4-dione (5e) from 3-Bromo-2-hydroxyketone (3e)

A solution of (**3e**) (3.19 g, 10 mmol) in benzene (3 mL) was added to the solution of $ZnCl_2$·*t*-BuOH·Et_3N (15 mmol) in benzene (7 mL) (prepared as described above) and the mixture was stirred for 1 h, allowed to stand at r.t. for 3 days, quenched with cold 5% aq H_2SO_4, and filtered. The crystalline product was washed successively with benzene, H_2O, and MeOH. Combined filtrates were placed in a separatory funnel, the organic layer was separated, washed twice with 5% aq NaCl, and dried (Na_2SO_4). The solvent was evaporated under vacuum, and the residue was crystallized from MeOH to afford an additional amount of product. Yield of **5e**: 1.25 g, 69%.

References and Notes

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