A Convenient Synthesis of Diketones via Alkylation of Alkyl Methyl Ketone Dimethylhydrazones

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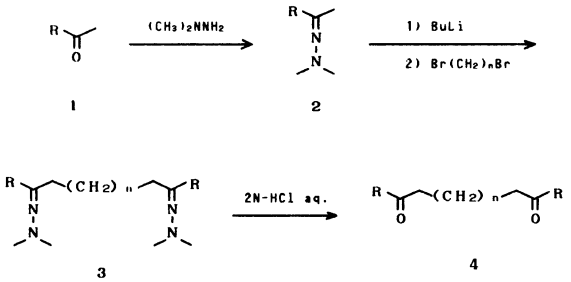
Synopsis. Symmetrical diketones were prepared by the reaction of the lithium salts of alkyl methyl ketone dimethylhydrazones with dibromoalkanes.

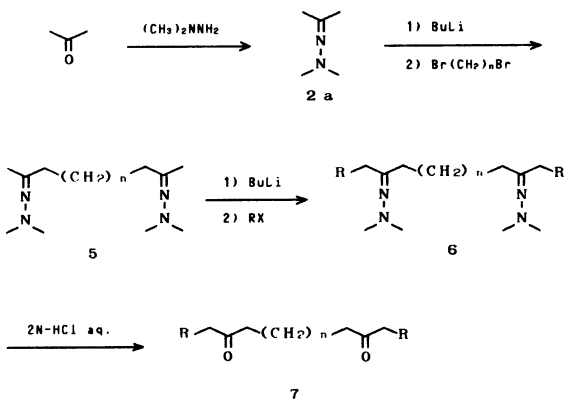
We previously reported a facile synthesis of unsymmetrical ketones by successive alkylation of acetone dimethylhydrazone,[1] and the application of this reaction to the synthesis of jasmones and the sex pheromone of the peach fruit moth.[1,2]

In this paper we wish to report a simple and convenient synthesis of the symmetrical diketones by alkylation of alkyl methyl ketone dimethylhydrazones[3] with dibromoalkanes. By the use of this method, 2,15-hexadecanedione, a precursor of muscone,[4] was also prepared in good yield.

The symmetrical diketones (**4**) were synthesized from a variety of alkyl methyl ketones (**1**) according to Scheme 1. For example, 2-octanone dimethylhydrazone (**2c**), readily available from 2-octanone and *N,N*-dimethylhydrazine using trifluoroacetic acid as a catalyst, was allowed to react with 1 equiv of butyllithium in THF at −5 °C under argon, followed by half equiv of 1,4-dibromobutane to give 7,14-icosanedione (**4f**) in 83% yield after hydrolysis. The results are listed in Table 1. 2,15-Hexadecanedione (**4b**) is a precursor of muscone,[4] which is one of the famous perfume materials.



Scheme 1.

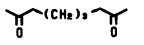
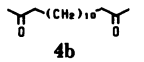
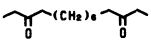
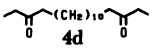
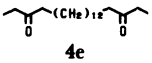
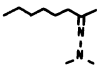
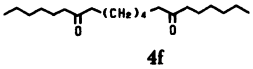
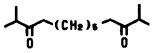
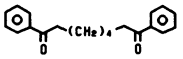
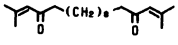
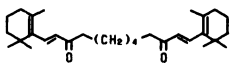


Scheme 2.

Furthermore, diketones (**7**) were also prepared by an alternative route starting from acetone dimethylhydrazone (**2a**), as shown in Scheme 2. For example, to the THF solution of the hydrazone (**2a**), 1 equiv of butyllithium and a half equiv of 1,6-dibromohexane was added successively. Then, dihydrazone was dilithiated by butyllithium, and 1-bromobutane was added to form dibutylated hydrazone, which was hydrolyzed using hydrochloric acid to afford 6,15-icosanedione (**7b**) in 84% yield. The other results are presented in Table 2.

By the methods described above, a variety of symmetrical diketones were prepared in satisfactory yields. No isomeric ketones were detected by TLC.

Table 1. Synthesis of Symmetrical Diketones (**4**) from Alkyl Methyl Ketone Dimethylhydrazones (**2**)

Run	Hydrazone	$Br(CH_2)_nBr$	Product	Yield/%[a]
1	 **2a**	$n=3$	 **4a**	54
2		$n=10$	 **4b**	66
3	 **2b**	$n=6$	 **4c**	67
4		$n=10$	 **4d**	84
5		$n=12$	 **4e**	77
6	 **2c**	$n=4$	 **4f**	83
7	 **2d**	$n=5$	 **4g**	76
8	 **2e**	$n=4$	 **4h**	91
9	 **2f**	$n=8$	 **4i**	76
10	 **2g**	$n=4$	 **4j**	68

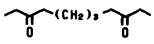
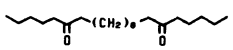
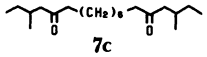
a) Isolated yields.

In conclusion, this synthetic method for symmetrical diketones has been found to be a prominent procedure in terms of good product yield, high regioselectivity of the alkylations, facile operations, and mild reaction conditions.

Experimental

The NMR spectra were measured on a Hitachi R-600 FT-NMR Spectrometer at 60 MHz using tetramethylsilane (δ=0.00) as an internal standard; chemical shifts are given in ppm. The IR spectra were recorded on a Hitachi 260-10 Infrared Spectrophotometer. The mass spectra (MS) were recorded on a Hitachi RM-50 GC-MS spectrometer. The GLC analysis was carried out on a Shimadzu GC-14A gas chromatograph, and the column chromatography was performed on Merck silica gel (230—400 mesh). Melting points were taken on a Yanagimoto micro melting point apparatus. No correction was made for melting and boiling points, and all the yields were isolated ones.

Table 2. Synthesis of Symmetrical Diketones (**7**) by the Successive Alkylation of Acetone Dimethylhydrazone (**2a**)

Run	$Br(CH_2)_nB$	RX	Product	Yield/%[a]
1	$n=3$	CH_3I	 **7a**	77
2	$n=6$		 **7b**	84
3	$n=6$		 **7c**	24

a) Isolated yields.

Preparation of Ketone Dimethylhydrazone (2). A typical procedure is as follows: a mixture of 2-octanone (50 mmol, 7.8 ml), *N,N*-dimethylhydrazine (75 mmol, 4.0 ml), trifluoroacetic acid (0.05 ml) and benzene (20 ml) was placed in a flask equipped with a trap used to remove water and refluxed for 2 h. After cooling to room temperature, the reaction mixture was added to brine and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and residual liquid was distilled to give 2-octanone dimethylhydrazone (**2c**) (7.47 g, 88% yield), bp 87 °C/20 Torr (1 Torr≈ 133.322 Pa).

^{1}H NMR, IR, and mass spectral data and boiling points of new hydrazones (**2**) are shown in Table 3.

General Procedure for the Preparation of Symmetrical Diketones (4). Butyllithium (4.4 mmol) was added via a syringe at −5 °C with stirring under argon to a solution of methyl ketone dimethylhydrazone (**2**) (4 mmol) in THF (15

Table 3. ^{1}H NMR, IR, and Mass Spectral Data of Dimethylhydrazones (**2**)

Compound	^{1}H NMR ($CDCl_3$, δ)	IR/cm^{-1}	MS m/z (M^+)	Bp/°C[a]
2f	1.83 (3H, s, CH_3), 1.92 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.51 (6H, s, NCH_3), 5.65—6.18 (1H, m, CH=)	2960, 1658, 1445, 1380, 1026	140	64 (20 Torr)
2g	1.06 (6H, s, CH_3), 1.20—1.28 (2H, m, CH_2), 1.54 (4H, d, CH_2), 1.73 (3H, s, $=CCH_3$), 2.13 (3H, s, $NCCH_3$), 2.50 (3H, s, NCH_3), 2.56 (3H, s, NCH_3), 6.12 (1h, d, CH=), 6.60 (1H, d, CH=)	1620, 1580, 1210, 1155, 1030, 980	234	Oil

a) Uncorrected boiling point.

Table 4. ^{1}H NMR, IR, and Mass Spectral Data of Diketones (**4** and **7**)

Compound	^{1}H NMR ($CDCl_3$, δ)	IR/cm^{-1}	MS m/z (M^+)	Bp/°C[a]
4d	1.05 (6H, t, CH_3), 1.18—1.86 (20H, m, CH_2), 2.39 (4H, t, $COCH_2$), 2.44 (4H, q, $C\underline{H}_2CH_3$)	2930, 1710, 1465, 1380, 1120	282	86—87
4e	1.05 (6H, t, CH_3), 1.17—1.85 (24H, m, CH_2), 2.39 (4H, t, $COCH_2$), 2.44 (4H, q, $C\underline{H}_2CH_3$)	2920, 1705, 1465, 1380, 1120	310	91—92
4f	0.90 (6H, t, CH_3), 1.07—1.95 (24H, m, CH_2), 2.40 (8H, t, $COCH_2$)	2940, 1710, 1475, 1390, 1090	310	82—83
4g	1.10 (12H, d, CH_3), 1.20—1.85 (10H, m, CH_2), 2.46 (4H, t, $COCH_2$), 2.30—2.95 (2H, m, CH)	2930, 1710, 1470, 1385, 1045	240	Oil
4i	1.16—2.05 (16H, m, CH_2), 1.88 (6H, s, CH_3), 2.14 (6H, s, CH_3), 2.40 (4H, t, $COCH_2$), 6.07 (2H, broad s, CH=)	2930, 1688, 1620, 1440, 1115, 1028	306	58—59
4j	1.08 (12H, s, CH_3), 1.35—1.88 (16H, m, CH_2), 1.78 (6H, s, $=CCH_3$), 2.10 (4H, m, $=CCH_2$), 2.60 (4H, t, $COCH_2$), 6.11 (2H, d, J=16Hz, =CH), 7.32 (2H, d, J=16Hz, =CH)	2925, 1695, 1665, 1610, 1460, 1365, 980		Oil
7a	1.05 (6H, t, CH_3), 1.27—1.85 (6H, m, CH_2), 2.40 (4H, t, $COCH_2$), 2.42 (4H, q, $C\underline{H}_2CH_3$)		184	
7b	0.90 (6H, t, CH_3), 1.10—1.90 (24H, m, CH_2), 2.40 (8H, t, $COCH_2$)	2920, 1700, 1465, 1380, 1085	310	76—77
7c	0.88 (6H, t, CH_3), 0.89 (6H, d, CH_3), 1.10—2.15 (18H, m, CH_2 and CH), 2.20—2.56 (8H, m, $COCH_2$)	2930, 1710, 1465, 1375, 1145, 1050	310	Oil

a) Uncorrected melting point.

ml). After 1 h dibromoalkane (2 mmol) was added at −5 °C; the reaction mixture was stirred for 15 h at room temperature before the addition of 2 mol dm^{-3} hydrochloric acid (15 ml). After standing for 15 h, the solution was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residure was purified by column chromatography over silica gel (hexane:ethyl acetate=8:2).

^{1}H NMR, IR, and mass spectral data and melting points of new diketones (**4**) are given in Table 4.

Preparation of Symmetrical Diketones (7) by Successive Alkylation Procedure. According to a method similar to that described above, using dibromoalkane and alkyl halide, the successive alkylations of acetone dimethylhydrazone (**2a**) and the hydrolysis were carried out. After the usual work up, column chromatography (hexane:ethyl acetate=9:1) gave the desired diketone.

^{1}H NMR, IR, and mass spectra data and melting points of new diketones (**7**) are given in Table 4.

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