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Free radical ring expansion and chain extension of 1,3-diketones

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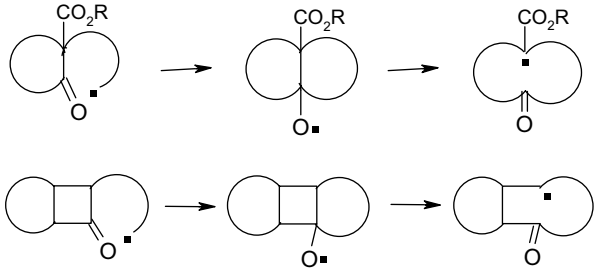
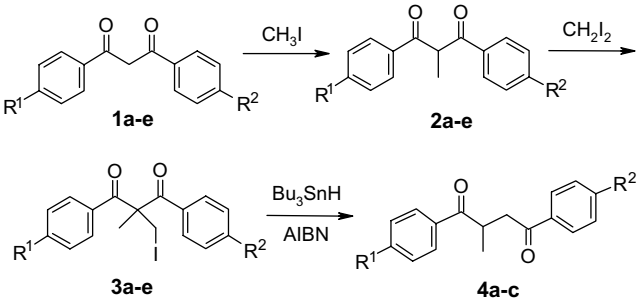
Abstract—Free radical-promoted one carbon ring expansion and chain extension of 1,3-diketones including 1,3-diarylpropane-1,3-diones and 2-aroyl-3,4-dihydro-2*H*-naphalen-1-one to generate corresponding 1,4-diketones are described.

Reactions to increase the chain length or ring size of a molecule with existing functional groups have general interest in organic synthesis.[1] Over the years, numerous ring expansion reactions have been developed.[2] Among them, the Dowd–Beckwith reaction of cyclic β-keto esters[3] and ring expansion of fused-cyclobutanones[4,5] are two well-known free radical reaction systems (Scheme 1). These reactions start with an alkyl radical cyclization to a carbonyl followed by a β-scission of the alkoxy radical to produce the desired product. The ester group and the strained-ring system are critical for the ring expansion process.[6] In this communication, we report examples of chain extension and ring expansion reactions of the 1,3-diketone system. A keto group of the 1,3-diketone plays a similar role as the ester group in the ring expansion of β-keto esters. Our method converts readily available 1,3-diketones to synthetically useful cyclic and acyclic 1,4-diketones. To our knowledge, such reactions have never been reported in the literature.



Scheme 1. Ring expansion of a β-keto ester radical and a cyclobutanone radical.

The one carbon chain extension of 2-(iodomethyl)-2-methyl-1,3-diphenyl-propane-1,3-dione **3a** was first attempted. This compound was prepared by methylation of 1,3-diphenylpropane-1,3-dione **1a** followed by iodomethylation of **2a** (Scheme 2). The free radical reaction of **3a** was promoted by Bu_3SnH with a catalytic amount of 2,2′-azobis(2-methylpropionitrile) (AIBN) as an initiator to give one carbon chain extension product **4a** in 76% yield. This method was then extended to other 2-(iodomethyl)-2-methyl-1,3-diarylpropane-1,3-diones with different substitution groups on the benzene rings (Table 1). We found these substitution groups have significant affect on the yield of iodomethylation reactions. 2-Methyl-1,3-bis(*p*-methoxyphenyl) and



Scheme 2. Chain extension of 2-(iodomethyl)-2-methyl-1,3-diarylpropane-1,3-diones **3**.

Keywords: 1,3-Diketones; 1,4-Diketones; Chain extension; Ring expansion; Radical reaction; Tributyltin hydride.
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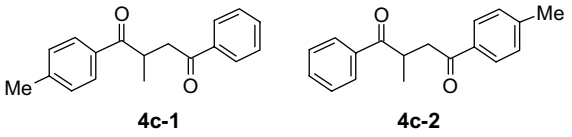
Table 1. Yields for iodomethylation products **3** and chain extension products **4**

Entry	Product[a]	R^1	R^2	Yield (%)[b]
1	**3a**	H	H	52
2	**3b**	*p*-CH_3	*p*-CH_3	49
3	**3c**	*p*-CH_3	H	42
4	**3d**	*p*-CH_3O	*p*-CH_3O	Trace
5	**3e**	*p*-Cl	*p*-Cl	Trace
6	**4a**	H	H	76
7	**4b**	*p*-CH_3	*p*-CH_3	64
8	**4c**[c]	*p*-CH_3	H	62

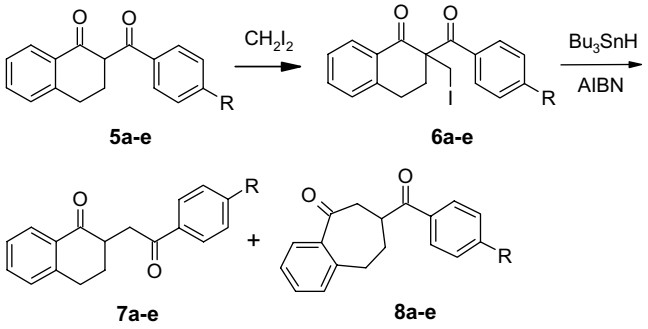
[a] All products were characterized by NMR and MS.
[b] Isolated yield after column chromatography.
[c] **4c** is a mixture of **4c-1** and **4c-2** (1:1).



2-methyl-1,3-bis(*p*-chlorophenyl)propane-1,3-diketones (**2d** and **2e**) were difficult to be iodomethylated. Iodomethylations of **2b** and **2c**, however, afforded desired products **3b** and **3c** in good yield. They were taken to radical reactions to produce corresponding products **4b** and **4c**. Since compound **3c** is an unsymmetric1,3-dione, a mixture of **4c-1** and **4c-2** was produced in a ratio of 1:1 (Table 1, entry 8). No regioselectivity was found for the chain extension reaction of **3c**. These two compounds were difficult to be isolated by chromatography.

We next explored radical reactions of a different kind of 1,3-diketones **6**. This system contains both cyclic and acyclic keto groups. Five radical precursors **6a**–**e** were prepared by iodomethylation of 2-aroyl-3,4-dihydro-2*H*-naphalen-1-ones of **5a**–**e** (Scheme 3). Results listed in Table 2 show that radical reaction of **6** gave two products; chain extension product **7** and ring expansion product **8**, compound **7** was the major product.[7] The mixture was separated by flash chromatography and the structure of each product was characterized by IR, NMR, and HRMS analyses.

A mechanism to explain two competitive radical reaction processes is outlined in Scheme 4. 3-*Exo* cyclizations of initial alkyl radical **9** to two different carbonyl groups generate cyclopropylalkoxy radicals **10a** and **10b**. Selective β-scissions of spirocyclopropylalkoxy radical **10a** and fused-cyclopropylalkoxy radical **10b** produce chain-extended radical **11a** and ring-expanded radical **11b**, respectively. Since the chain-extension was found to be the major process, it suggests that cyclization of alkyl radical **9** to the acyclic carbonyl is superior to the cyclic carbonyl. This is probably due to the difference of stereo hindrance associated with these two cyclization processes.

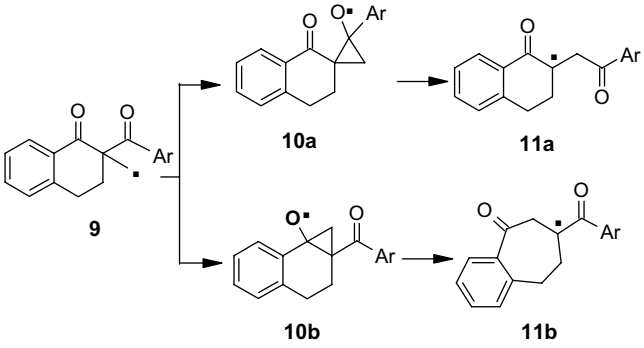


Scheme 3. Ring expansion and chain extension of 2-aroyl-3,4-dihydro-2*H*-naphalen-1-ones **6**.

Table 2. Yields for alkylation products **6** and radical reaction products **7** and **8**

Entry	Product[a]	R	Yield (%)[b]
1	**6a**	H	53
2	**6b**	*p*-CH_3	58
3	**6c**	*p*-CH_3O	59
4	**6d**	*p*-Cl	62
5	**6e**	*p*-Br	56
6	**7a**	H	68[c]
7	**7b**	*p*-CH_3	52
8	**7c**	*p*-CH_3O	46
9	**7d**	*p*-Cl	55
10	**7e**	*p*-Br	51
11	**8a**	H	26[c]
12	**8b**	*p*-CH_3	18
13	**8c**	*p*-CH_3O	23
14	**8d**	*p*-Cl	13
15	**8e**	*p*-Br	10

[a] All products were characterized by NMR and MS.
[b] Isolated yield after column chromatography.
[c] Analyzed by HPLC.



Scheme 4. Free radical ring expansion and chain extension of a 2-aroyl-3,4-dihydronaphalen-1(2*H*)-one radical.

In summary, we have explored the one carbon ring expansion and chain extension of two different kinds of 1,3-diketones. For 1,3-diarylpropane-1,3-dione system, the chain extension reaction has high yield. It is good for symmetric 1,3-diketones. Reactions of 2-aroyl-3,4-dihydro-2*H*-naphalen-1-one system produce a mixture of chain-extension and ring-expansion products. The chain extension is the major process.

General procedures for alkylation:[8] Preparation of **3a**—2-Methyl-1,3-diphenylpropane-1,3-dione **2a** (1.19 g,

5 mmol), anhydrous potassium carbonate (1.38 g, 10 mmol), tetrabutylammonium bromide (0.64 g, 2 mmol) and dry toluene (15 mL) were added to 50 mL three-necked flask and the mixture was refluxed for 5 h under the nitrogen atmosphere. The mixture was then cooled to 40 °C, diiodomethane (1.47 g, 5.5 mmol) was added, stirred at 40 °C for 2 h and refluxed for another 2 h. The mixture was cooled to room temperature, filtered, and washed with diethyl ether. After removal of the solvent, the residue was purified by chromatography on silica gel eluted with petroleum ether/ethyl acetate (20:1) to afford **3a** in 52% yield, mp 88–90 °C, IR (KBr)*v* 1677 (C═O), 1654 (C═O). ^{1}H NMR ($CDCl_3$) δ 7.86–7.34 (m, 10H, $2C_6H_5$), 3.86 (s, 2H, CH_2), 1.76 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 198.0, 136.1, 133.9, 129.6, 129.3, 63.4, 24.7, 14.2. HRMS calcd for $C_{17}H_{15}O_2I$ 378.0117; found 378.0118 (M^+).

General procedures for free radical one-carbon chain extension: Preparation of **4a**—Compound **3a** (76 mg, 0.20 mmol), AIBN (10 mg, 0.06 mmol), tributyltin hydride (116 mg, 0.40 mmol) and dry benzene (22 mL) were added to a 50 mL three-necked flask. The mixture was refluxed for 0.5 h under the nitrogen atmosphere. The solvent was removed, the residue was dissolved in dichloromethane (25 mL), washed with 10% aqueous potassium fluoride, dried over $MgSO_4$, and concentrated. The residue was then dissolved in acetonitrile (25 mL), washed with petroleum ether, and concentrated. The crude product was purified by silica gel chromatography eluted with petroleum ether/ethyl acetate (15:1) to afford **4a** in yield 76%, mp 96-98 °C. IR (KBr) *v* 1678 (C═O). ^{1}H NMR ($CDCl_3$) δ 8.07–7.45 (m, 10H, $2C_6H_5$), 4.20 (m, 1H, CH), 3.75 (dd, 1H, J_1 = 8.60 Hz, J_2 = 18.00 Hz), 3.14 (dd, 1H, J_1 = 4.80 Hz, J_2 = 18.00 Hz), 1.29 (d, 3H, CH_3, J = 6.80 Hz); ^{13}C NMR ($CDCl_3$) δ 203.8, 198.9, 137.3, 136.7, 133.6, 133.4, 129.2, 129.1, 129.0, 128.6, 42.8, 36.8, 18.4. HRMS calcd for $C_{17}H_{16}O_2$ 252.1150; found 252.1144 (M^+).

Acknowledgments

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7. Analytical data for **7a**: mp 80–82 °C. ^{1}H NMR ($CDCl_3$) δ 8.05–7.25 (m, 9H, C_6H_4 and C_6H_5), 3.89–3.84 (m, 1H, CH), 3.61–3.15 (m, 2H, CH_2), 3.02–2.96 (m, 2H, CH_2), 2.32–1.97 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 199.5, 199.0, 144.6, 137.4, 133.9, 133.6 132.7, 129.3, 129.1, 128.6, 127.9, 127.1, 44.7, 39.5, 30.0, 29.9. HRMS (M^+) calcd for $C_{18}H_{16}O_2$ 264.1150; found 264.1130 (M^+). Analytical data for **8a**: mp 68–70 °C. ^{1}H NMR ($CDCl_3$): δ 7.91–7.25 (m, 9H, C_6H_4 and C_6H_5), 3.88–3.81 (m, 1H, CH), 3.26–3.16 (m, 2H, CH_2), 2.96–2.92 (m, 2H, CH_2), 2.29–2.09 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 203.4, 201.4, 142.0, 138.6, 135.9 133.9, 133.0 130.4, 129.4, 129.3, 129.0, 127.5, 43.4, 40.4, 31.9, 29.8; HRMS calcd for $C_{18}H_{16}O_2$ 264.1150; found 264.1148 (M^+).
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