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$AlCl_3$-Mediated Aldol Cyclocondensation of 1,6- and 1,7-Diones to Cyclopentene and Cyclohexene Derivatives

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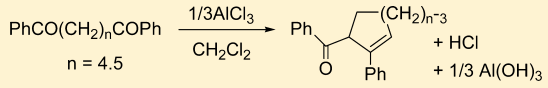
Supporting Information

ABSTRACT: Exactly 1/3 mol of $AlCl_3$ is sufficient to cyclize 1 mol of 1,ω-dibenzoylbutane (or pentane) to a cyclopentenone (or hexenone) derivative in high yield at room temperature in 40 min to several hours. This condensation is driven by removing elements of water as HCl and $Al(OH)_3$, and the product enones are exclusively unconjugated, unlike the base-catalyzed condensations providing thermodynamically more stable conjugated enones.



INTRODUCTION

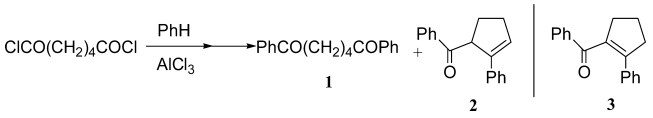
The aldol condensation is one of the fundamental organic reactions for C−C bond formation.[1] Although in the infancy of organic chemistry protic acids were used as catalysts for aldol condensation,[2] after discovery of base-catalyzed reaction,[3] acid catalysts have been used only sporadically in special cases.[4] Here we report that $AlCl_3$ can serve as a Lewis acid catalyst as well as a dehydrating agent for aldol cyclocondensation.

RESULTS AND DISCUSSION

Side Reaction in a Friedel−Crafts Reaction. Preparation of 1,4-dibenzoylbutane **1** by the Friedel−Crafts reaction of adipoyl dichloride with benzene in the presence of $AlCl_3$ is a standard Organic Syntheses (OS) procedure, providing 75−81% yield.[5a] However, a drastic decrease in the yield of **1** was observed if the reaction mixture was not quenched after the specified reaction time of 2 h, when the $AlCl_3$ complex of the product crystallized out, but was left standing for an extended period of time. Then, the crystalline complex dissolved to a dark homogeneous liquid, which gave a tarry material upon aqueous workup. This was nothing but a failure but attracted our attention, because the TLC analysis of the product mixture (SiO_2, hexane/chloroform/EtOAc 4:1:0.2) showed a large spot of much lower polarity (R_f 0.7) in addition to a small spot for the desired dione **1** (R_f 0.4). Since no mention is made of such a byproduct in the OS procedure[5a] or in its original paper,[5b] we separated the reaction mixture by preparative TLC. The compound isolated as colorless needles (mp 99−100 °C) was characterized by means of elemental analysis and ^1H and ^{13}C NMR, IR, and EI-mass spectral data and found to be 1-phenyl-2-benzoylcyclopentene **2** (Scheme 1), a known compound formed in low yields by base-catalyzed aldol condensation of **1**[6] or by reduction of 1,4-dibromo-1,4-dibenzoylbutane with Zn−NaI.[7]

Apparently this side product is formed by an acid-catalyzed aldol condensation of **1**.[8] The product, however, was not the more stable conjugated enone **3**, which is the predominant isomer in the base-catalyzed reaction,[6c] but an unconjugated enone **2**.[9] Although the use of $AlCl_3$ as an acid catalyst has been reported for the aldol condensation of benzaldehyde and acetophenone or their derivatives,[10] the reactions require a long time (days) for completion, otherwise suffer from low yields, and have been considered useful only when base-sensitive substituents are present. We decided, therefore, to examine the reaction in detail. As described below the aldol condensation mediated by $AlCl_3$ is found to have several unique aspects and furnishes cyclopentene and cyclohexene derivatives in high yields in short reaction times by optimization of the reaction conditions.

Scheme 1. Side Reaction in the Preparation of 1,4-Dibenzoylbutane 1



Effect of $AlCl_3$. Although $AlCl_3$ alone is not soluble in anhydrous CH_2Cl_2,[11] when **1** was added in a molar ratio of 1:1 and the mixture was stirred at room temperature, it dissolved in a few minutes and gave a clear yellow solution of a **1**−$AlCl_3$ complex (if quenched at this stage, **1** was recovered unchanged). After several minutes, a turbidity appeared and gradually increased to form a white precipitate. In the meantime, TLC analysis (silica gel/4:1 hexane/EtOAc) showed a new spot for **2**, which increased as the reaction proceeded. At the same time, a small spot was noticed between the two spots, which was assumed to be that for the intermediate aldol **4**, because the spot disappeared when **1** was consumed after 45 min. Aqueous workup of the reaction mixture and MPLC separation provided 91% yield of **2** (Scheme 2).

The amount of $AlCl_3$ was found to have a significant effect on this reaction. Use of 2 equiv of $AlCl_3$ led to total recovery of **1** even after stirring for 1 day at room temperature. This suggests that the complexation of $AlCl_3$ occurs with both

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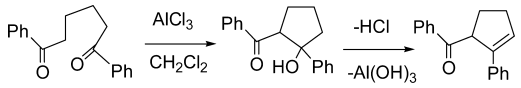
Scheme 2. Aldol Condensation of Dibnzoylbutane



carbonyl groups rapidly and completely, leaving no free carbonyl group for the next step of the reaction. On the other hand, a catalytic amount was insufficient, providing only a small amount of **2**. When the amount of $AlCl_3$ was increased to 1/3 equiv, the reaction was found to be completed in less than 1 h. The best yield (97%, 99% corrected for the recovery of **1**) was obtained when a cold solution of **1** in CH_2Cl_2 was mixed with 1/3 equiv of $AlCl_3$ and stirred at 0 °C for 1 h (only trace of **2** was detected at this stage) and then at room temperature for 40 min. As the reaction progressed, evolution of HCl and formation of a white precipitate were observed. The precipitate was suspected to be $Al(OH)_3$,[12] and its amount was measured by collecting on a glass filter and drying (100 °C/0.1 mmHg for 48 h) until no more loss in weight, providing almost the expected amount (31% excess) as $Al(OH)_3$. Therefore, the water formed in this aldol condensation is removed as $Al(OH)_3$ and HCl, thus driving the reaction irreversibly. This is in contrast to the usual acid-catalyzed aldol condensation, where dehydration is done by heating.[13]

The fact that only one of the three Cl atoms of $AlCl_3$ is needed in the condensation for each molecule of **1** led us to examine the reaction using an Al species with only one active Cl. For this purpose a dialkoxide $ClAl(OR)_2$, which can be obtained by reacting $AlCl_3$ with alcohol (ROH), may be used. In order to ensure formation of the bisalkoxide, we selected diols, which are expected to form chelates. We tried chiral ethyl tartarate and binaphthol hoping for asymmetric induction. Though no enantiomeric excess was observed (HPLC, Chiralpack AD-H), high yields of **2** were realized in both cases (77% and 94%, respectively). An interesting finding made in the course of these experiments is the effect of HCl on the reaction. Namely, when the reagent solution was prepared from $AlCl_3$ and ethyl tartarate in CH_2Cl_2 without cooling, the reagent was much less active than the solution made under cooling. Since the temperature of the solution was kept below 40 °C by vaporization of CH_2Cl_2, change in the composition of the Al species seemed unlikely. The difference, therefore, was considered to arise from the loss of HCl from the solution as bubbles when the solution was made without cooling. Conversely, when CH_2Cl_2 was saturated with HCl, the reaction of **1** with $AlCl_3$ was accelerated considerably. Thus, the necessity of HCl for the reaction is evident, but since HCl is released in the course of the reaction as described above, the effect of HCl is noticeable only at the initial stage of the reaction.

Effect of Other Lewis Acids. We examined several other readily available Lewis acids for this reaction as shown in Table 1.

$ZnCl_2$ formed the precipitate of a complex with **1**, and no further changes were observed (entry 3). The reaction with $SiCl_4$ was slow and incomplete after 24 h and gave low yields (at best 6%) of **2** (entries 3−6). The use of $SnCl_4$ (0.3 equiv) resulted in 64% yield of **2** after 24 h (entry 6). Further extension of the reaction time or increased amount of $SnCl_4$ resulted in side reactions. Although $BF_3{\cdot}OEt_2$ alone (1.1 equiv) was inefficient, providing only 45% yield of **2** with 50% recovery of **1** after 24 h (entry 16),[14] the use of HCl-saturated CH_2Cl_2 remarkably accelerated the reaction and **2** was obtained in 91% yield in 2 h (entry 18). This fact also suggests the participation of HCl in the condensation.

Table 1. Effects of Lewis Acids on Reaction with 1 in CH_2Cl_2 at Room Temperature

				products, yield (%)		
entry	Lewis acid	mol ratio to **1**	reaction time	**1**	**2**	**4**[b]
1	$AlCl_3$	0.33	40 min	2.0	96.6	nd
2		1.1	45 min	2.4	91.2	nd
3	$ZnCl_2$	0.5	24 h	~100		
4	$SiCl_4$	0.6	48 h	42.6	7.8	nd
5		1.0	48 h	71.0	4.6	nd
6		1.0	24 h	84.5	6.3	nd
7	$SnCl_4$	0.3	3 h	70.4	15.8	1.2
8		0.3	24 h	20.7	64.9	tr
9		0.6	24 h	15.2	54.4	nd
10		1.0	3 h	25.4	46.0	tr
11	$TiCl_4$	0.3	3 h	61.0	12.2	3.4
12		0.6	2 h	64.3	19.7	1.1
13		0.6	24 h	40.0	33.4	2.7
14	BF_3	0.3	48 h	40.9	45.0	nd
15		0.6	24 h	56.1	32.7	nd
16		1.1	24 h	50.1	44.5	nd
17		0.3[a]	48 h	20.8	68.0	nd
18		1.1[a]	2 h	3.7	90.7	nd

[a]In HCl-saturated CH_2Cl_2, [b]nd, not detected; tr, trace

When $TiCl_4$ was used, **1**−$TiCl_4$ adduct was formed as an orange-colored precipitate, and its conversion to **2** occurred only slowly, which did not go to completion even after 24 h (0.6 equiv $TiCl_4$, 33% yield of **2** with 40% recovery of **1**, entry 13). $TiCl_4$, however, was found to be useful in the preparation of the intermediate aldol **4**. Though $TiCl_4$ alone gave **4** as colorless needles (mp 100−101 °C) in 3% yield as shown in Table 1, the yield of **4** could be increased by utilizing a solution of $Ti(OEt)_2Cl_2$ prepared by treating a solution of $TiCl_4$ in 1,2-dichloroethane with 2 equiv of EtOH (MeOH was not suitable because the bismethoxide precipitated out). In order to reduce the possible effect of HCl on elimination as described above, the solution was purged with nitrogen. When **1** was added to the light yellow bisethoxide solution, smooth reaction took place to give an equilibrium mixture of **1** and **4** (almost 1:1 ratio upon TLC analysis) after 1 h. Since the acid-sensitive nature of **4** for its reversion to **1** was recognized,[15] aqueous workup was conducted under weakly basic conditions, and the product mixture was immediately separated by MPLC. Still, **4** was obtained in only 8% yield (62% corrected for the recovery of **1**). Although **4** is unstable in solution, it is stable in crystalline state, allowing its X-ray crystallographic analysis.[16] As shown in Figure 1, **4** has a C═O···H−O hydrogen-bonded structure, which is the most stable one by conformational searches and DFT calculations as detailed in Supporting Information.

Selective Formation of Unconjugated Enones. In this cycloaldol condensation unconjugated enone **2** is produced exclusively, unlike the base-catalyzed condensation where conjugated enone **3** is predominant.[6] This is in accord with the thermodynamic stability estimated by molecular calculations: **3** is more stable than **2** by 2.1 kcal/mol [Gaussian09, B3LYP/6-311+G(2d,p); details in Supporting Information].

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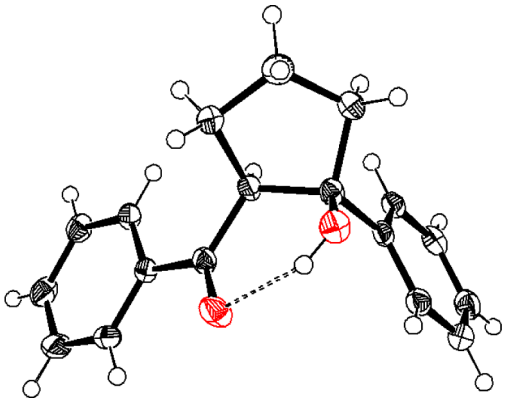
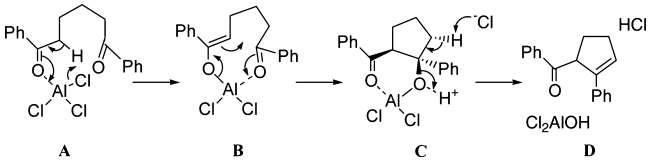


Figure 1. X-ray structure of aldol **4**.

As a matter of fact, if the reaction conditions were not right (excess Lewis acids and longer reaction times), conjugated **3** was isolated in small amounts as a low melting solid (reported[6] mp 44 or 54 °C). As shown by the fact that exclusive formation of **2** could be achieved in 99% yield in short reaction times, **3** was not formed directly but by acid-catalyzed isomerization of **2**. The effectiveness of $AlCl_3$ in the catalytic isomerization was low, and only 12% conversion was observed when a solution of **2** in CH_2Cl_2 was stirred in the presence of 30 mol % $AlCl_3$ at room temperature for 24 h. The most effective reagent for the isomerization was found to be $TiCl_4$, which induced complete isomerization of **2** after 20 h, providing **3** in 81% isolated yield.

Proposed Mechanism. Evidently, the conventional mechanism of aldol condesnation in hydroxylic solvents cannot be applied for this reaction in the nonhydroxylic solvent CH_2Cl_2, The experimental facts described above led to the tentative mechanistic proposal shown in Scheme 3.

Scheme 3. Proposed Mechanism for the Condensation



After complexation of $AlCl_3$ with one of the carbonyl groups of **1** occurs to give **A**, an Al enolate **B** is formed with releasing HCl. Then, the enolate moiety adds intramolecularly on the other carbonyl group to form a five-membered ring. The process is apparently assisted by coordination to the Al ion as an Al aldolate **5** (**C**). The structure of **5** is assumed to be similar to that of **4** in Figure 1, showing the presence of C═O···H−O hydrogen bonding. Actually, the most favored configuration of **5** as optimized by DFT calculations (B3LYP/LANL2DZ) from several possible starting structures was that shown in Figure 2 (see Supporting Information). In the next elimination step, the two hydrogens, Ha and Hb, which are *anti periplanar* to the C−O bond to be cleaved, are candidates for abstraction by a base (Figure 2), leading to unconjugated or conjugated enone, respectively. However, Ha is less hindered, and thus, the formation of unconjugated **2** is kinetically favored over the thermodynamically more stable conjugated **3**. Since involvement of HCl in the reaction is suggested as described above, Cl^- is assumed to be the species attacking at Ha of the protonated Al aldolate as depicted in **C**.

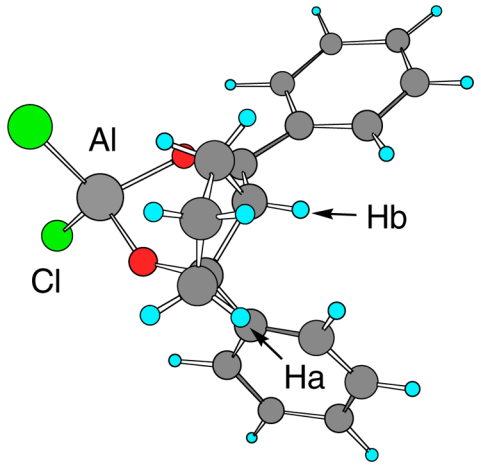
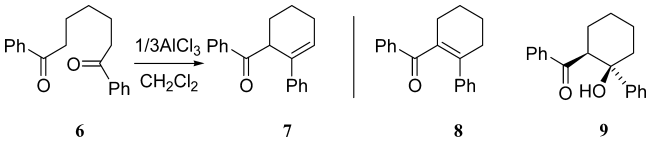


Figure 2. DFT (B3LYP/LANL2DZ)-optimized structure for the Al aldolate **5**.

Extension to Six-Membered Ring Formation. This cyclocondensation reaction was successfully extended to construct a six-membered ring, though the reaction was considerably slower. Thus, the reaction of 1,5-dibenzoylpentane **6** with 1/3 equiv $AlCl_3$ was almost complete after 6 h to give unconjugated **7** (colorless needles, mp 107−108 °C)[17] in yield of 90% without formation of conjugated **8** (Scheme 4).

Scheme 4. Cycloaldol Condensation To Form Six-Membered 7



Acceleration effect of HCl was also present, and the reaction time was shortened to 2 h to give 87% yield of **7**. In contrast to the acid-sensitive five-membered ring aldol **4**, six-membered ring aldol **9** (colorless plates, mp 127−128 °C), which has been isolated in small amount by base-catalyzed aldol condensation),[18] was readily prepared in 74% yield by using $TiCl_4$. The structure of **9** is predicted to be that shown with a C═O···H−O hydrogen bond by molecular calculations (conformational searches and DFT optimizations), which were remarkably successful in reproducing the X-ray structure of **4** (Supporting Information),

In contrast to the thermodynamically favored five- and six-membered ring formation, attempts to form strained rings with 4, 7, and 8 members gave either only recovery of most of the starting diones under the mild conditions as for the five- and six-membered rings or complex mixtures of products under forcing conditions (heating for a prolonged time).

Intermolecular Condensation. Intermolecular self-condensation of acetophenone did not proceed at all. However, the reaction of acetophenone with benzaldehyde proceeded at room temperature in the presence of 0.36 equiv of $AlCl_3$. After 20 h, the reaction gave a mixture containing a chloride **10**[19] (isolable in 15% yield), **11**, and the starting materials (Scheme 5). Due to the thermal instability of **10**, distillation of the product mixture gave **11** in 61% yield. The formation of chloride **10** is assumed to be formed by nucleophilic attack of a chloride ion on the Al aldolate (**E**).

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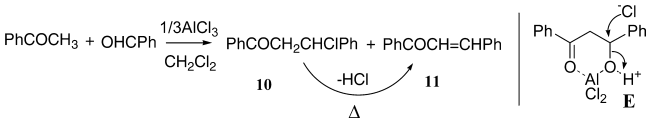
Scheme 5



Scheme 6. Reaction of $PhCO(CH_2)_4COR$ 12 with $AlCl_3$ in CH_2Cl_2

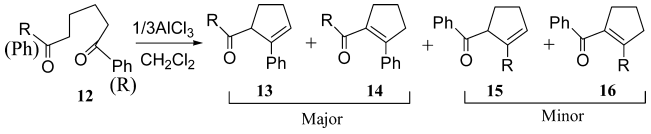


Table 2. Aldol Condensation of $PhCO(CH_2)_4COR$ 12 with 1/3 $AlCl_3$ in HCl-Saturated CH_2Cl_2

			yield (%)		
entry	R	reation time (h at rt)	**13** + **14** (ratio)	**15**	**16**
1	Me	5	71.9 (56:44)	*a*	4.8
2	Me	5	68.9 (61:39)	*a*	*a*
3	Me	5	73.7 (65:35)	*a*	2.7
4	Me	4.5	65.1 (67:33)	*a*	3.3
5	Et	23	27.4 (60:40)	*a*	*a*
6	Et	4	73.1 (79:21)	*a*	*a*
7	Et	5	87.0 (80:20)	2.5	*a*

[a]A mixture of compounds in a trace amount.

Cyclization of $PhCO(CH_2)_4COR$. In order to extend the scope of this condensation, we studied the cases where one of the Ph groups of **1** was replaced with an alkyl group R (Me or Et) as shown in Scheme 6, and the results are collected in Table 2.

Since the reaction of $PhCO(CH_2)_4COR$ **12** (R = Et) with 1/3 equiv $AlCl_3$ in CH_2Cl_2 was found to be much slower than that of **1** or **6** in a preliminary experiment, the reaction was conducted in HCl-saturated CH_2Cl_2 at room temperature. However, **12** did not disappear completely after 5 h by TLC analysis, and then the mixture was stirred overnight (23 h). After aqueous workup, the product mixture was separated by MPLC. The major product, eluted as overlapping peaks after a small peak, was found to be a mixture of unconjugated **13** and conjugated **14**, both having a RCO group instead of PhCO, in a ratio of 60:40 by ^1H and ^{13}C NMR analysis (entry 5). The poor selectivity for the unsubstituted **13** was considered to be due to the long reaction time, because if the reaction is slow, **13** formed in the course of the reaction would be isomerized to **14** by remaining $AlCl_3$ as discussed above. Therefore, the later reactions were quenched after 4−5 h, when a small spot of **12** was still detected by TLC analysis. Then the ratios were much improved to ca. 80:20 (entries 6 and 7), though complete control could not be made. On the other hand, in the cases of **12** (R = Me) the ratios of unconjugated to conjugated were lower and at best ca. 65:35 (entries 3 and 4) under the same reaction conditions. Thus, in contrast to the almost complete selectivity for unconjugated **2** and **7**, the ratio for **13** decreased from Et to Me. These results may be understood in terms of decrease in hindrance to the approach of a Cl ion to Hb in the Al aldolate **5** (Figure 2) when its PhCO group is replaced with a less bulky EtCO or even smaller MeCO group.

As shown in Table 2, the other possible isomers with a PhCO group were also obtained in small amounts (3% yields) as a peak preceding the major peaks of **13** and **14** in MPLC separation. The only assignable compounds were **16** for R = Me and **15** for R = Et, because the minor products were obtained in only small amounts and often as a mixture of several compounds.

Since both PhCO- and RCO-containing isomers were obtained for $PhCO(CH_2)_4COR$, this aldol cyclization reaction may also be applied to bis(alkanoyl)butanes $RCO(CH_2)_4COR'$. Unfortunately, we have not confirmed this possibility as yet because of the rather difficult accessibility of 1,6-diones, particularly with dissimilar alkyl groups.[20]

Autoxidation of the Unconjugated Enones. To be noted is the unexpectedly high susceptibility of **13** and **14** toward oxygen. Though the enone mixtures (R = Me and Et) were obtained as colorless mobile liquids right after separation, they turned to gel-like materials after a day, if not stored with exclusion of air. The decomposed samples were complex mixtures without **13** and **14** as revealed by ^1H NMR spectroscopy. In fact, at the beginning of the studies on the reaction of **12** we were not aware of this susceptibility problem and were puzzled by the low yield of 27% for **13** and **14** (entry 5).

Although **2** is much more stable than **13** and **14**, its sample stored for several years was found to contain a new compound together with brown decomposed matter. The structure of this compound, isolated as colorless needles (mp 155−156 °C), was elucidated by X-ray crystallography[16] to be 2-phenyl-3-benzoylcyclopentanone **17**[21] as shown in Figure 3. Apparently

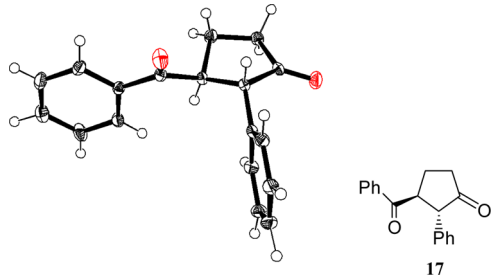


Figure 3. X-ray Structure of Air-oxidation Product **17**.

2 was oxidized with singlet oxygen formed by activation with light.[22] As a preliminary experiment, the solution of **2** in benzene was exposed to sunlight for 2 days until most of **2** disappeared. Though the reaction was not efficient, with formation of many unidentifiable products, **17** was obtained in 44% yield.

CONCLUSION

Examination of the side product in the Friedel−Crafts reaction led to a new efficient aldol condensation for cyclization to five- and six-membered rings under mild reaction conditions as summarized in Table 3.

Though the reaction is not catalytic, it requires inexpensive $AlCl_3$ in only 1/3 molar amount. Particularly noteworthy is the fact that thermodynamically less stable unconjugated enones **2** and **7** were formed selectively, unlike in the base-catalyzed aldol condensation.

EXPERIMENTAL SECTION

Starting Materials. *1,4-Dibenzoylbutane* ***1*** *and 1,5-Dibenzoylpentane* ***6***. Prepared according to the OS procedure[5] by using adipic acid and pimelic acid, respectively, and recrystallized from EtOH.

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Table 3. Results for the $AlCl_3$-Mediated[a] Aldol Cyclocondensation in CH_2Cl_2

entry	dione	reaction time (at rt)	product(s) (yield)
1	**1**	40 min	**2** (97%)
2	**6**	6 h (2 h[b])	**7** (90%, 87%[b])
3	$PhCO(CH_2)_4COMe$	5 h[b]	**13** + **14** (R = Me, 65:35) (74%)
4	$PhCO(CH_2)_4COEt$	5 h[b]	**13** + **14** (R = Et, 80:20) (87%)

[a]One-third equiv of $AlCl_3$ per mole of the dione was used. [b]In HCl-saturated CH_2Cl_2.

1-Phenylheptane-1,6-dione ($PhCO(CH_2)_4COMe$). Prepared by Raney Ni reduction of 2-benzoyl-5-acetylthiophene: colorless needles, mp 45−46 °C (lit.[20b] mp 44−45 °C). ^1H NMR (270 MHz, $CDCl_3$) δ 7.99−7.92 (m, 2H), 7.60−7.50 (m, 1H), 7.50−7.42 (m, 2H), 2.99 (t, J = 6.9 Hz, 2H), 2.50 (t, J = 6.9 Hz, 2H), 2.15 (s, 3H), 1.82−1.60 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 208.7, 199.9, 136.8, 132.9, 128.5, 127.9, 43.4, 38.2, 29.8, 23.6, 23.3.

1-Phenyloctane-1,6-dione ($PhCO(CH_2)_4COEt$). Prepared by Raney Ni reduction of 2-benzoyl-5-propanoylthiophene, distilled at 100 °C/0.2 mmHg: colorless platelets, mp 33−34 °C (lit.[23] mp 84 °C). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found C 76.92 H 8.28. ^1H NMR (270 MHz, $CDCl_3$) δ 7.99−7.91 (m, 2H), 7.60−7.51 (m, 1H), 7.51−7.42 (m, 2H), 2.99 (t, J = 6.9 Hz, 2H), 2.47 (t, J = 6.9 Hz, 2H), 2.44 (q, J = 7.3 Hz, 2H), 1.81−1.60 (m, 4H), 1.05 (t, J = 7.3 Hz, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 211.3, 199.9, 136.8, 132.9, 128.5, 127.9, 42.1, 38.2, 35.8, 23.6, 23.4, 7.7.

1-Phenyl-5-benzoylcyclopentene 2. *Best Procedure.* To a solution of 1,4-dibenzoylbutane **1** (799.0 mg, 3.0 mmol) in 10 mL of CH_2Cl_2 cooled in an ice bath was added powdered $AlCl_3$ (144 mg 1.08 mmol) in one portion. After 10 min of stirring, all $AlCl_3$ dissolved to form a pale yellow solution. After 1.5 h only a small spot for **2** appeared on TLC analysis. The bath was removed, and the reaction mixture was allowed to reach room temperature. After 10 min a white granular precipitate was formed. After 40 min the precipitate began to assume a greenish yellow tinge and TLC indicated the disappearance of **1**. Then, the reaction was quenched by addition of water and extracted with chloroform. After drying ($MgSO_4$), the extract was filtered through a short column of silica gel, concentrated, and separated by MPLC (silica gel, 4:1:0.25 hexane/chloroform/EtOAc) to give 719.3 mg (96.6% yield) of **2** as colorless needles (hexane), mp 99−100 °C (lit.[6a] mp 98 °C). From the later fractions **1** (15.8 mg, 2.0%) was recovered, making the yield of **2**, corrected for the recovery, 98.6%. Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 86.99; H, 6.47. ^1H NMR (270 MHz, $CDCl_3$) δ 8.06 (d, J = 6.9 Hz, 2H), 7.63−7.55 (m, 1H), 7.55−7.43 (m, 2H), 7.36−7.12 (m, 5H), 6.47 (m, 1H), 4.95 (m, 1H), 2.78−2.45 (m, 3H), and 2.19−2.05 (m, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 201.1, 141.6, 136.5, 135.6, 133.1, 130.1, 128.7, 128.4, 127.1, 125.8, 53.5, 32.4, 30.1.

Large-Scale Preparation. To 1,4-dibenzoylbutane **1** (7.99 g, 30 mmol) in 50 mL of CH_2Cl_2 cooled in an ice water bath was added $AlCl_3$ (powdered, 1450 mg, 10.9 mmol). After 10 min the yellow solution was allowed to warm to room temperature. After 5 min, the solution became reddish in color and a white precipitate started to form. After 30 min **1** disappeared as judged by TLC (SiO_2, 4:1 hexane/EtOAc). The reaction was quenched by addition of water, and the product was extracted with chloroform (2×). The combined extract was dried ($MgSO_4$), passed through a short column of silica gel, and evaporated. The residue was crystallized from hexane/acetone to form colorless needles (4.149 g), The mother liquor was separated by MPLC (there was no peak for **1**, and therefore, simple recrystallization is sufficient) to give 2.615 g, making total of 6.764 g (90.8%).

Isomerization of 2 to 3 with $TiCl_4$. To a solution of **2** (300 mg, 1.21 mmol) in CH_2Cl_2 (5 mL) was added $TiCl_4$ (50 μL, 0.46 mmol, 0.38 equiv) in one portion at room temperature. Immediate deep brown coloration occurred. After 20 h, the dark brown solution was quenched with water and extracted with chloroform (3×). A brown extract was dried ($MgSO_4$), filtered through a short column of silica gel, and subjected to MPLC separation to give a pale brown liquid (solidified on cooling, 244 mg, 81.3%), which was identical with **3** prepared by base-catalyzed reaction of **1**.[6c] ^1H NMR (270 MHz, $CDCl_3$) δ 7.74 (d, J = 6.9 Hz, 2H), 7.41−7.31 (m, 1H), 7.30−7.19 (m, 2H), 7.19−6.99 (m, 5H), 3.07−2.87 (m, 4H), and 2.20−2.04 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 198.4, 146.1, 137.4, 136.5, 135.9, 132.7, 129.2, 128.1, 127.9, 127.8, 127.6, 37.9, 37.6, 22.5.

1-Phenyl-2-benzoylcyclopentanol 4. Addition of EtOH (360 μL, 6.2 mmol) to a solution of $TiCl_4$ (340 μL, 3.1 mmol, 1.03 equiv) in 5 mL of $ClCH_2CH_2Cl$ at room temperature resulted in an immediate exothermic reaction with evolution of HCl. The HCl dissolved in the solution was purged by bubbling nitrogen for 5 min. To the light yellow solution was added **1** (799.0 mg, 3.0 mmol) in 10 mL of $ClCH_2CH_2Cl$. The reaction mixture was stirred for 1 h at room temperature and then cooled in an ice−water bath for 1 h before quenching with a cold saturated $NaHCO_3$ solution. The product was extracted with chloroform, and the extract was dried (Na_2SO_4 instead of acidic $MgSO_4$) and passed through a short column of silica gel and evaporated. The crystalline residue was recrystallized from hexane/chloroform to remove most of **1** (286.2 mg). The mother liquor was immediately separated by MPLC (SiO_2, hexane/chloroform/EtOAc 3:1:0.25) to give **2** (7.7 mg, 1.0%), **4** (65.0 mg, 8.1%), and **1** (408.4 mg, total of 694.6 mg, 86.9%). Recrystallization of **4** from hexane gave colorless needles, mp 100−101 °C. Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.20; H, 6.78. ^1H NMR (270 MHz, $CDCl_3$) δ 7.86 (d, J = 6.9 Hz, 2H), 7.61−7.36 (m, 5H), 7.33−7.23 (m, 2H), 7.23−7.10 (m, 1H), 5.40 (d, J = 1.0 Hz, 1H, OH, exchangeable with D_2O), 4.09 (dd, J = 10.2, 10.6 Hz, 1H), 2.42−1.89 (m, 6H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 205.4, 145.2, 136.8, 133.7, 128.6, 128.3, 128.1, 126.7, 124.9, 84.5, 54.6, 42.7, 30.4, 22.7.

1-Phenyl-6-benzoycyclohexene 7. To 1,5-dibenzoylpentane **6** (841.1 mg, 3.0 mmol) in 10 mL of HCl-saturated CH_2Cl_2 cooled in an ice bath was added powdered $AlCl_3$ (143 mg 1.07 mmol, 0.357 equiv). After 5 min all $AlCl_3$ was dissolved to give a faintly yellow solution with slight turbidity, Then the bath was removed, and the reaction was allowed to reach room temperature. After 2 h the reaction was complete judging from TLC. Then the reaction was quenched with water, and the product was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and passed through a short column of silica gel. After evaporation of the solution, the residue was separated by MPLC (SiO_2, hexane/chloroform/EtOAc 3:1:0.25) to give **7** as colorless needles (681.5 mg, 86.6%), mp 107−108 °C (lit.[18b] mp 107−108 °C). ^1H NMR (270 MHz, $CDCl_3$) δ 8.01 (d, J = 7.3 Hz, 2H), 7.60−7.51 (m, 1H), 7.51−7.40 (m, 2H), 7.30−7.08 (m, 5H), 6.39 (t, J = 3.7 Hz, 1H), 4.72 (br t, J = 4.9 Hz, 1H), 2.45−2.20 (m, 2H), 2.20−1.95 (m, 2H), 1.76−1.61 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 201.0, 141.6, 136.1, 135.1, 132.9, 128.7, 128.5, 128.3, 126.7, 125.3, 45.1, 27.3, 25.6, 18.7.

1-Phenyl-2-benzoylcyclohexene 8. Prepared in 28.4% yield according to Gao et al.[18b] for comparison purpose. Colorless plates (hexane/acetone), mp 79−80 °C (lit.[6b] 78−79 °C). ^1H NMR (270 MHz, $CDCl_3$) δ 7.68 (d, J = 7.3 Hz, 2H), 7.35−7.27 (m, 1H), 7.25−7.16 (m, 2H), 7.11−7.94 (m, 5H), 2.56−2.40 (m, 4H), 1.98−1.71(m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 201.3, 141.7, 139.8, 136.7, 135.2, 132.3, 129.1, 127.9, 127.8, 127.1, 30.8, 28.0, 22.8, 22.0.

1-Phenyl-2-benzoylcyclohexanol 9. To 1,5-dibenzoylpentane **6** (841.1 mg, 3.0 mmo) in 10 mL of HCl-saturated CH_2Cl_2 was added $TiCl_4$ (150 μL, 1.36 mmol, 0.45 equiv) at room temperature. The immediate orange coloration faded in 5 min to deep yellow. After 20 min TLC showed considerable formation of **9** (ca. 1:1 area ratio as compared to **6**). After 24 h the reaction was almost complete and was quenched by addition of water. The product was extracted with chloroform. The extract was washed with water, dried($MgSO_4$), filtered through a short column (SiO_2), and evaporated. The residue was separated by MPLC (SiO_2, 4:1:0.25 hexane/chloroform/EtOAc) to give **7** (31.8 mg, 4.0%) and **9** (623 mg, 74.1%) as colorless plates (hexane/acetone), mp 127−128 °C (lit.[17a] mp 127−128 °C), and **6**

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(148 mg, 17.6%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.81 (d, J = 7.3 Hz, 2H), 7.55−7.44 (m, 3H), 7.43−7.34 (m, 2H), 7.26−7.16 (m, 2H). 7.13−7.05 (m, 1H), 5.15 (d, J = 2.6 Hz, 1H, OH as confirmed by D_2O exchange), 3.99 (dd, J = 11.9, 3.3 Hz, 1H), 2.15−1.78 (m, 5H), 1.78−1.38 (m, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 206.5, 148.4, 136.0, 133.5, 128.6, 128.1, 128.1, 126.4, 124.4, 74.5, 50.7, 40.5, 27.1, 25.6, 21.6.

Reaction of Acetophenone and Benzaldehyde. *Preparation of Chalcone* ***11***. To a mixture of acetophenone (600 mg, 4.99 mmol) and benzaldehyde (560 mg, 5.27 mmol) in 10 mL of CH_2Cl_2 was added powdered $AlCl_3$ (360 mg, 2.70 mmol, 0.54 equiv). Considerable exothermic reaction occurred, and a deep orange solution resulted. After 2 h the reaction was quenched with water and extracted. The extract was washed with water, dried ($MgSO_4$), and filtered through a short column of silica gel. After evaporation, the residue was distilled to give **11** as a pale yellow liquid at 240−245 °C/0.8 mmHg (633 mg, 60.8%), which solidified on standing.

Isolation of Chloride ***10***. To a solution of acetophenone (600 mg, 4.99 mmol) and benzaldehyde (530 mg, 4.99 mmol) in 5 mL of CH_2Cl_2 was added $AlCl_3$ (250 mg, 1.87 mmol, 0.374 equiv) in an ice−water bath. After 5 min the bath was removed and stirred at room temperature for 20 h. Then the reaction was quenched by addition of water and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), filtered through a short column of silica gel, and subjected to MPLC separation. However, since only partial separation was achieved, the fractions containing the products were separated by fractional crystallization from hexane to give 180.2 mg (14.8%) of **10** as white platelets, mp 111−112 °C (dec) [lit.[18] mp 110−112 °C (dec)]. The oily mother liquor contained chalcone **11** as well as aceophenone and benzaldehyde.

Aldol Condensation of 1-Phenylheptane-1,6-dione PhCO-$(CH_2)_4$COMe. To a solution of 1-phenylheptane-1,6-dione (612.8 mg 3.0 mmol) in 10 mL of HCl-saturated CH_2Cl_2 was added $AlCl_3$ (138 mg, 1.03 mmol) at room temperature. After 5 min almost all $AlCl_3$ dissolved, and a turbid pale tan solution was formed. After 5 h of stirring, the reaction was quenched by addition of water, and the product was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and filtered through a short column (SiO_2). After evaporation, the residue was separated by MPLC to give minor enone **16** (R = Me) followed by a mixture of enones **13** and **14** (R = Me) as an inseparable peak.

1-Methyl-2-benzoylcyclopentene ***16*** *(R = Me).* Colorless liquid, 15.4 mg (2.7%). Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.88; H, 7.46. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.80−7.72 (m, 2H), 7.57−7.49 (m, 1H), 7.48−7.39 (m, 2H), 2.86−2.70 (m, 2H), 2.62−2.46 (m, 2H), 1.92 (quint, J = 7.6 Hz, 2H), 1.68 (sept, J = 0.68, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 197.2, 150.0, 139.1, 136.1, 132.2, 128.8, 128.3, 40.4, 35.7, 22.1, 16.7.

Mixture of 1-Phenyl-5-acetylcyclopentne ***13*** *(R = Me) and 1-Phenyl-2-acetyl-cyclopentene* ***14*** *(R = Me) (65:35 Mixture by NMR).* Colorless liquid (165 °C/1.0 mmHg), 411.3 mg (73.7%). Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.66; H, 7,53. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.42−7.18 (m, 5H), 6.43−6.38 (m, 0.65 × 1H), 4.05−3.96 (m, 0.65 × 1H), 2.92−2.76 (m, 0.65 × 2H), 2.73−2.56 (m, 0.65 × 2H), 2.47−2.23 (m, 0.35 × 2H), 2.17−2.05 (m, 0.35 × 2H), 2.03 (s, 0.65 × 3H), 1.96 (t, J = 7.3 Hz, 0.35 × 2H),1.91 (s, 0.35 × 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 211.2, 200.0, 152.9, 141.6, 139.5, 137.9, 135.3, 130.4, 128.5, 128.4, 128.1, 127.5, 127.4, 125.7, 60.0, 41.5, 35.0, 32.5, 29.7, 28.0, 26.3, 21.7.

Aldol Condensation of 1-Phenyloctane-1,6-dione PhCO-$(CH_2)_4$COEt. To a solution of 1-phenyloctane-1,6-dione (218 mg, 1.0 mmol) in 3 mL of HCl-satd CH_2Cl_2 was added $AlCl_3$ (47 mg, 0.35 mmol) at room temperature. After 15 min all $AlCl_3$ dissolved, and then a white turbid solution was formed. After 5 h the reaction was quenched by addition of water, and the product was extracted with chloroform. The extract was dried ($MgSO_4$), filtered through a short column (SiO_2), and evaporated. the residue was separated by MPLC to give minor enone **15** (R = Et) and major enone as a mixture of **13** and **14** (R = Et).

1-Ethyl-5-benzoylcyclopentene ***15*** *(R = Et).* Pale yellow liquid, 5.1 mg (2.5%) mixed with some other compounds that could not be removed due to the small sample amount. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.05−7.96 (m, 2H), 7.63−7.11 (m, 3H), 6.21−6.17 (m, 1H), 4.30 (dd, J = 8.6, 3.3 Hz, 1H), 2.77−2.66 (m, 2H), 2.60−2.48 (m, 2H), 2.28−2.18 (m, 2H), 2.98 (t, J = 7.2 Hz, 3H). ^{3}C NMR (67.8 MHz, $CDCl_3$) δ 201.3, 142.4, 137.2, 133.3, 132.4, 128.8, 128.8, 128.6, 128.4, 126.8, 126.1, 125.5, 87.4, 57.5, 41.5, 33.4, 33.2, 32.5, 29.3, 23.4, 22.8, 10.4.

Mixture of 1-Phenyl-5-propanoylcyclopentene ***13*** *(R = Et) and 1-Phenyl-2-propanoylcyclopentene* ***14*** *(R = Et) (80:20 mixture by NMR).* Colorless liquid (Kugel-Rohr distillation, 140 °C/0.25 mmHg, 173.9 mg, 87.0%). Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.63; H, 8.06. EI MS calcd 200.12, found 200.10. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.40−7.16 (m, 5H), 6.40−6.35 (m, 0.80 × 1H), 4.08−3.99 (m, 0.80 × 1H), 2.90−1.91 (m, 0.20 × 8H + 0.80 × 6H), 0.93 (t, J = 7.2 Hz, 0.80 × 3H), 0.91 (t, J = 7.2 Hz, 0.20 × 3H). ^{3}C NMR (67.8 MHz, $CDCl_3$) δ 213.3, 203.8, 150.3, 141.5, 139.0, 137.7, 135.4, 130.3, 128.4, 128.2, 127.9, 127.4, 127.2, 125.6, 59.1, 40.7, 35.4, 34.9, 32.4, 32.1, 28.3, 21.8, 8.1, 7.7.

Photo-oxygenation of 2 to 2-Phenyl-3-benzoylcyclopenanone 17. A solution of **2** (100 mg) in 2 mL of benzene was exposed to sunlight. After 2 days, TLC analysis revealed disappearance of **2** and appearance of two major spots, one for **17** and the other for a more polar compound. The yellow product mixture was separated by MPLC to give 46.9 mg (44.1%) of **17** as colorless prisms (chloroform), mp 155−156 °C (lit.[21a] mp 159−159.5 °C). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.91 (d, J = 6.9 Hz, 2H), 7.63−7.51 (m, 1H), 7.51−7.38 (m, 2H)., 7.33−7.20 (m, 3H), 7.20−7.10 (m, 2H), 4.26 (m, J = 10.6 Hz, 1H), 4.06 (dd, J = 10.6 Hz. J = 1.0 Hz, 1H), 2.81−2.61 (m, 1H), 2.61−2.41 (m, 2H), 2.19−1.99 (m, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 199.5, 137.4, 135.9, 133.6, 128.8, 128.7, 128.6, 128.4, 127.2, 57.9, 52.0, 38.2, 26.2.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of the ^{1}H and ^{13}C NMR spectra, the coordinates and energies of the calculated structures of **2**−**5** and **9**, and the X-ray structure files (cif format) for **4** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Drying over weakly acidic $MgSO_4$ overnight destroyed all of **4**. Although **4** itself has not been reported, its electron-rich *p*-methoxy derivative, which is more stable, has been isolated: Clausen, C.; Wartchow, R.; Butenschön, H. *Eur. J. Org. Chem.* **2001**, 93−113. For recent examples of acid-catalyzed formation of cyclic aldols, though with extra ester and carbonyl groups present, see: Truong, P.; Shanahan, C. S.; Doyle, M. P. *Org. Lett.* **2012**, *14*, 3608−3611.

(16) Crystallographic data (excluding structure factors) for the structure reported in this paper are available as Supporting Information

(17) Base-catalyzed aldol condensation of **6**: (a) $NaNH_2$/toluene: conjugated **8** (mp 91−92 °C) and unconjugated **7** (mp 110 °C). Bauer, E. *Ann. Chim. Appl.* **1914**, *1*, 377−393. (b) NaOEt/EtOH: **8** (mp 91−92 °C, 11.4% yield) and **7** (mp 107−108 °C, 4.4% yield). Gao, J.; Chen, W.; Jiang, K. *Acta Chim. Sin.* **1982**, *40* (1), 91−93. In an old paper by Kipping and Perkin it is stated that although **6** was recovered unchanged after treatment with conc H_2SO_4 for 3 days, warming **6** with P_2O_5 gave a compound with composition $C_{19}H_{18}O$ in low yield. Kipping, S.; Perkin, W. H., Jr. *J. Chem. Soc.* **1890**, *57*, 13−28 The reported melting point (110−111 °C) indicates that the product they obtained could be unconjugated **7** (mp 107−108 °C)..

(18) (a) By NaOEt-catalyzed reaction of **6**, **9** (mp 127−128 °C) has been obtained in 1.3% yield: Gao, J.; Chen, W.; Jiang, K. *Acta Chim. Sin.* **1982**, *40* (1), 91−93. (b) As a side product from reaction of 1,5-dibenzoyl-1,5-dibromopentane and Li_2Se, **9** (mp 128 °C) has been isolated: Honda, E.; Iwamura, T.; Watanabe, S.; Kataoka, T.; Muraoka, O.; Tanabe, G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 529−536.

(19) It was reported that when a 1:1 mixture of acetophenone and benzaldehyde was saturated with HCl for a few days and the crystalline mass deposited was recrystallized, **10** was obtained as white plates, which melted at 119−120 °C on rapid heating or 110−112 °C on slow heating with decomposition to **11** and HCl. Claisen, L.; Claparede, A. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2460−2468.

(20) We have not arrived at an efficient general synthetic method for 1.6-diones in terms of the yield and purity of the products as well as safety in the preparation procedures, after examining several of the literature methods we thought promising, such as (a) Katritzky, A. R.; Huang, Z.; Fang, Y.; Prakash, I. *J. Org. Chem.* **1999**, *64*, 2124−2126. (b) Nishinaga, A.; Rindo, K.; Matsuura, T. *Synthesis* **1986**, 1038−1041.

(21) (a) By acid-catalyzed rearrangement of 1-phenyl-5-benzoylcyclopentene oxide, **17** (mp 159−159.5 °C): Babcock, S. H., Jr.; Fuson, R. C. *J. Am. Chem. Soc.* **1936**, *58*, 2325−2326. (b) By action of peracids on **2**, **17** (mp 157−158 °C): Wasserman, H. H.; Gorbunoff, M. J. *J. Am. Chem. Soc.* **1958**, *80*, 4568−4573.

(22) For photo-oxygenation of simple olefins, see: Shimizu, N.; Bartlett, P. D. *J. Am. Chem. Soc.* **1976**, *98*, 4193−4200. In the present case no sensitizer was needed.

(23) Itoh, K.; Nakanishi, S.; Otsuji, Y. *J. Organometallic Chem.* **1994**, *473*, 215−224.