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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 10 Jun 2014

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The AlCl₃-Mediated Aldol Cyclocondensation of 1, 6- and 1, 7-Diones to Cyclopentene and Cyclohexene Derivatives

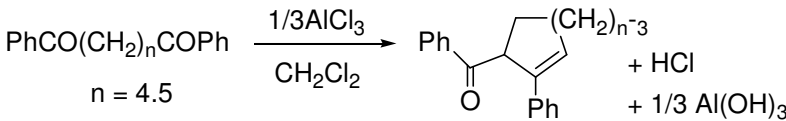
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TOC Graphic Abstract



ABSTRACT: Exactly 1/3 mole of AlCl₃ is sufficient to cyclize 1 mole 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

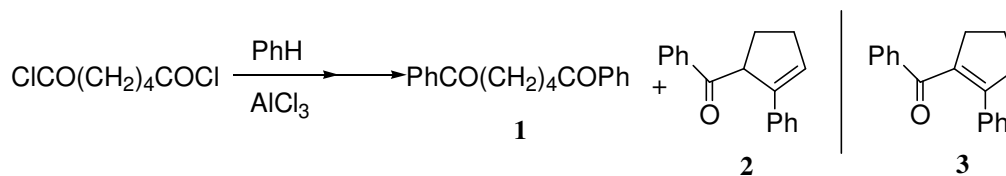
The aldol condensation is one of the fundamental organic reactions for C-C bond formation.¹ Although in the infancy of organic chemistry protic acids were used as catalysts for aldol condensation,² after discovery of base-catalyzed reaction,³ acid catalysts have only been used sporadically in special cases.⁴ Here we report that AlCl₃ can serve as a Lewis acid catalyst as well as a dehydrating agent for aldol cyclocondensation.

RESULTS AND DISCUSSION

A 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 AlCl₃ 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 AlCl₃ complex of the product crystallized out, but 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 (SiO₂, hexane-chloroform-EtOAc 4 : 1 : 0.2) showed a large spot of much less 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 ¹³C 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

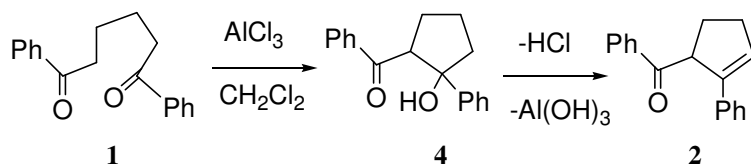
Scheme 1. A Side Reaction in the Preparation of 1,4-Dibenzoylbutane 1



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.

The Effect of AlCl₃. Although AlCl₃ alone is not soluble in anhydrous CH₂Cl₂,¹¹ 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**-AlCl₃ 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. Aldol Condensation of Dibenzoylbutane



The amount of AlCl_3 was found to have a significant effect on this reaction. Use of 2 molar equivalents 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 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 mol equivalent, 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 mol equivalent 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 $\text{Al}(\text{OH})_3$ ¹² and its amount was measured by collecting on a glass filter and drying (100 °C/0.1 mmHg for 48 h)

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7 until no more loss in weight, providing almost the expected amount (31% excess) as
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10 $\text{Al}(\text{OH})_3$. Therefore, the water formed in this aldol condensation is removed as $\text{Al}(\text{OH})_3$ and
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13 HCl , thus driving the reaction irreversibly. This is in contrast to the usual acid-catalyzed
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16 aldol condensation, where dehydration is done by heating.¹³
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20 The fact that only one of the three Cl's of AlCl_3 is needed in the condensation for each
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23 molecule of **1** led us to examine the reaction using an Al species with only one active Cl. For
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26 this purpose a dialkoxide $\text{ClAl}(\text{OR})_2$, which can be obtained by reacting AlCl_3 with alcohol
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29 (ROH) , may be used. In order to ensure formation of the bisalkoxide we selected diols,
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32 which are expected to form chelates. We tried chiral ethyl tartarate and binaphthol hoping
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35 for asymmetric induction. Though no enantiomeric excess was observed (HPLC, Chiralpack
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38 AD-H), high yields of **2** were realized in both cases (77% and 94%, respectively). An
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41 interesting finding made in the course of these experiments is the effect of HCl on the
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44 reaction. Namely, when the reagent solution was prepared from AlCl_3 and ethyl tartarate in
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47 CH_2Cl_2 without cooling, the reagent was much less active than the solution made under
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50 cooling. Since the temperature of the solution was kept below 40 °C by vaporization of
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CH₂Cl₂, 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 CH₂Cl₂ was saturated with HCl, the reaction of **1** with AlCl₃ 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.

Table 1. Effects of Lewis Acids on Reaction with 1 in CH₂Cl₂ at Room Temperature

entry	Lewis acid		reaction time	products, yield (%)		
	mol ratio to 1			1	2	4
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*	48 h	20.8	68.0	nd
18		1.1*	2 h	3.7	90.7	nd

*: in HCl saturated CH₂Cl₂, nd: not detecte, tr: trace

ZnCl₂ formed the precipitate of a complex with **1** and no further changes were observed (entry 3). The reaction with SiCl₄ was slow and incomplete after 24 h and gave low yields (at best 6%) of **2** (entries 3-6). The use of SnCl₄ (0.3 eq) resulted in 64% yield of **2** after 24 h (entry 6). Further extension of the reaction time or increased amount of SnCl₄ resulted in side reactions. Although BF₃·OEt₂ alone (1.1 eq) was inefficient, providing only 45% yield of **2** with 50% recovery of **1** after 24 h (entry 16),¹⁴ the use of HCl-saturated CH₂Cl₂ 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.

When TiCl₄ was used, **1**-TiCl₄ adduct was formed as an orange-colored precipitate and its conversion to **2** occurred only slowly, which did not go completion even after 24 h (0.6 eq TiCl₄, 33% yield of **2** with 40% recovery of **1**, entry 13). TiCl₄, however, was found to be useful in the preparation of the intermediate aldol **4**. Though TiCl₄ 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)₂Cl₂ prepared by treating a solution of TiCl₄ in 1,2-dichloroethane with 2 eq 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.

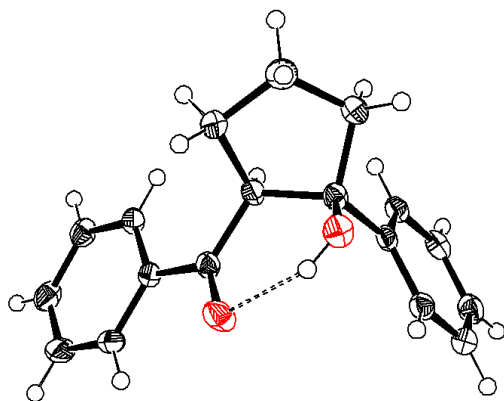


Figure 1. The X-ray Structure of Aldol 4.

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].

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 (reported⁶ 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 condensation in hydroxylic solvents cannot be applied for this reaction in the non-hydroxylic solvent CH_2Cl_2 . The experimental facts described above led to a tentative mechanistic proposal shown in Scheme 3.

Scheme 3. Proposed Mechanism for the Condensation

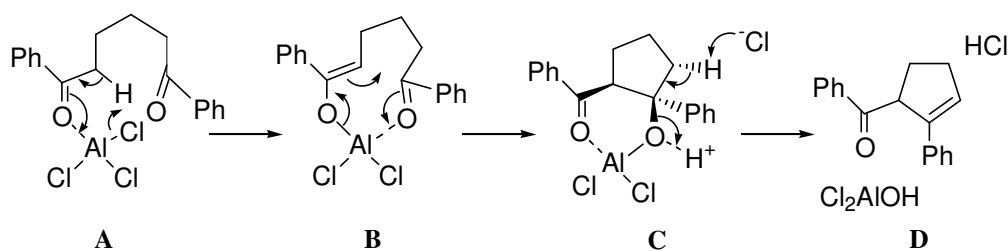
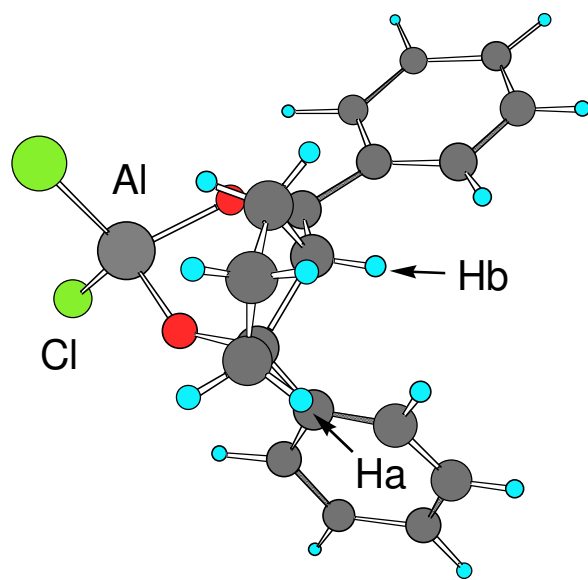


Figure 2. DFT (B3LYP/LANL2DZ)-optimized Structure for the Al Aldolate **5.**



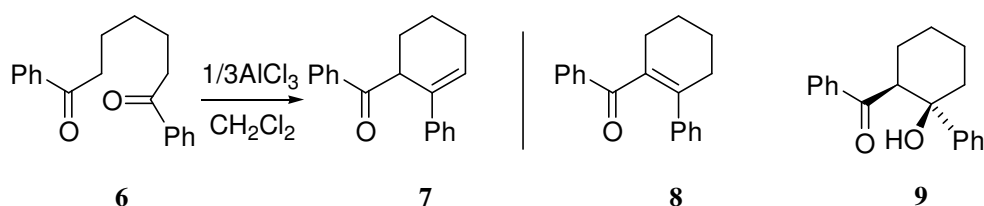
After complexation of AlCl_3 with one of the carbonyl groups of **1** occurs to give **A**, an Al enolate **B** is formed with releasing HCl . Then, the enolate moiety adds intramolecularly on the other carbonyl group to form a five-membered ring. The process is apparently assisted by coordination to 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 $\text{C}=\text{O} \cdots \text{H}-\text{O}$ 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**.

Extension to 6-Membered Ring Formation. This cyclocondensation reaction was successfully extended to construct a 6-membered ring, though the reaction was considerably slower. Thus, the reaction of 1,5-dibenzoylpentane **6** with 1/3 AlCl₃ 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**. 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 5-membered ring aldol **4**, 6-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),

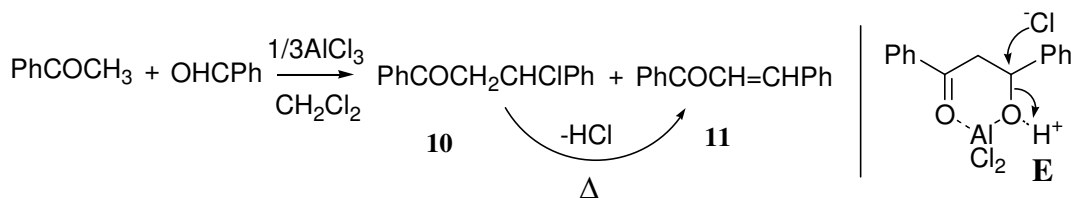
Scheme 4. The Cycloaldol Condensation to Form 6-Membered **7**



In contrast to the thermodynamically favored 5- and 6-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 5- and 6-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 eq 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**).

Scheme 5



Cyclization of $\text{PhCO}(\text{CH}_2)_4\text{COR}$. 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.

Scheme 6. The reaction of PhCO(CH₂)₄COR **12 with AlCl₃ in CH₂Cl₂**

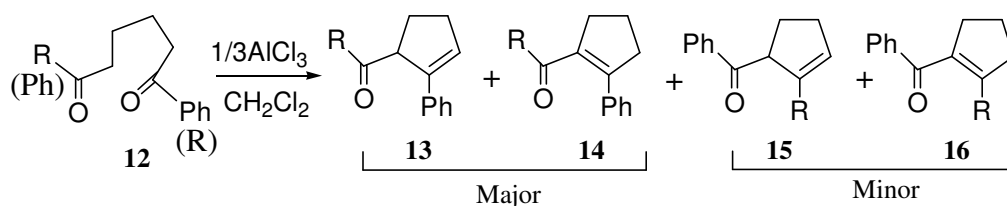


Table 2. Aldol condensation of PhCO(CH₂)₄COR **12 with 1/3 AlCl₃ in HCl-satd CH₂Cl₂**

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

--: A mixture of compounds in a trace amount.

Since the reaction of PhCO(CH₂)₄COR **12** (R = Et) with 1/3 eq AlCl₃ in CH₂Cl₂ was found to be much slower than that of **1** or **6** in a preliminary experiment, the reaction was conducted in

HCl-saturated CH₂Cl₂ 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 ¹³C 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 AlCl₃ 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 H_b 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.

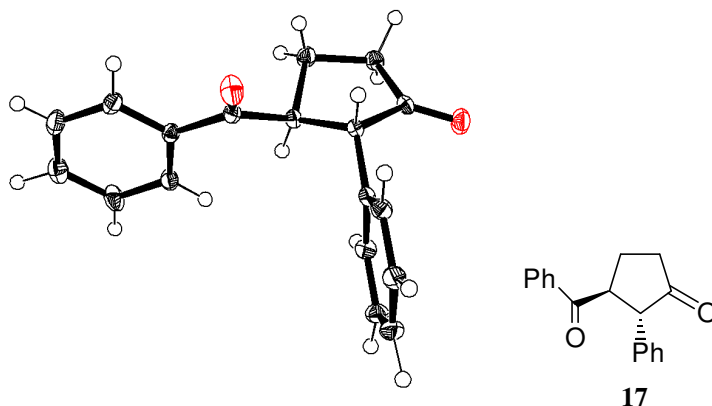
Since both PhCO- and RCO-containing isomers were obtained for PhCO(CH₂)₄COR, this aldol cyclization reaction may also be applied to bis(alkanoyl)butanes RCO(CH₂)₄COR'. Unfortunately, we have not confirmed this possibility as yet because of rather difficult accessibility of 1,6-diones, particularly with 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 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 crystallography¹⁶ to be 2-phenyl-3-benzoylcyclopentanone **17**²¹ as shown in Figure 3. Apparently **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.

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



CONCLUSION

The examination of the side product in the Friedel-Crafts reaction led to a new efficient aldol condensation for cyclization to 5- and 6-membered rings under mild reaction conditions as summarized in Table 3.

Table 3. Results for the AlCl_3 -mediated* 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 ^{**})	7 (90%, 87% ^{**})
3	PhCO(CH ₂) ₄ COMe	5 h ^{**}	13 + 14 (R = Me, 65 : 35) (74%)
4	PhCO(CH ₂) ₄ COEt	5 h ^{**}	13 + 14 (R = Et, 80 : 20) (87%)

* 1/3 molar amount of AlCl₃ per mole of the dione was used.

**In HCl-saturated CH₂Cl₂.

Though the reaction is not catalytic, it requires inexpensive AlCl₃ in only 1/3 molar amount.

Particularly noteworthy is the fact that thermodynamically less stable unconjugated enones **2**

and **7** were formed selectively unlike the base-catalyzed aldol condensation.

EXPERIMENTAL SECTION

Starting materials.

1,4-Dibenzoylbutane 1 and 1,5-dibenzoylpentane 6. Prepared according to the OS

procedure⁵ by using adipic acid and pimelic acid, respectively, and recrystallized from EtOH.

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7 *1-Phenylheptane-1,6-dione* ($\text{PhCO}(\text{CH}_2)_4\text{COMe}$). Prepared by Raney Ni reduction of
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9
10 2-benzoyl-5-acetylthiophene, colorless needles mp 45-46 °C (lit.²² mp 44-45°C). ^1H NMR
11
12 (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 =
13
14 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,
15
16 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.
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23
24 *1-Phenyloctane-1,6-dione* ($\text{PhCO}(\text{CH}_2)_4\text{COEt}$): Prepared by Raney Ni reduction of
25
26
27 2-benzoyl-5-propanoylthiophene, distilled at 100 °C/0.2 mmHg, colorless platelets, mp
28
29 33-34 °C (lit.²³ mp 84 °C). Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_2$: C, 77.03; H, 8.31. Found C 76.92
30
31 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,
32
33 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,
34
35 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,
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37 128.5, 127.9, 42.1, 38.2, 35.8, 23.6, 23.4, 7.7.
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51 **1-Phenyl-5-benzoylcyclopentene** **2**. *The best procedure:* To a solution of **1**,
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54 4-dibenzoylbutane **1** (799.0 mg, 3.0 mmol) in 10 mL CH_2Cl_2 cooled in an ice bath was added
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powdered AlCl_3 (144 mg 1.08 mmol) in one portion. After stirring for 10 min 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 $\text{C}_{18}\text{H}_{16}\text{O}$: 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 CH₂Cl₂ cooled in an ice water bath was added AlCl₃ (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 (SiO₂, 4:1 hexane-EtOAc). The reaction was quenched by addition of water and the product was extracted with chloroform (2x). The combined extract was dried (MgSO₄), 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 TiCl₄. To a solution of **2** (300 mg, 1.21 mmol) in CH₂Cl₂ (5 mL) was added TiCl₄ (50 µL, 0.46 mmol, 0.38 eq) 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 (3x). A brown extract was dried (MgSO₄), 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, CDCl₃) 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). ¹³C NMR (67.8 MHz, CDCl₃) 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 μ L, 6.2 mmol) to a solution of TiCl₄ (340 μ L, 3.1 mmol, 1.03 eq) in 5 mL of ClCH₂CH₂Cl 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 ClCH₂CH₂Cl. 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 NaHCO₃ solution. The product was extracted with chloroform and the extract was dried (Na₂SO₄ instead of acidic MgSO₄) 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 (SiO₂,

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 C₁₈H₁₈O₂: C, 81.17; H, 6.81. Found C, 81.20; H, 6.78. ¹H NMR (270 MHz, CDCl₃) 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 D₂O), 4.09 (dd, *J* = 10.2, 10.6 Hz, 1H), 2.42-1.89 (m, 6H). ¹³C NMR (67.8 MHz, CDCl₃) 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-benzoylcyclohexene 7: To 1,5-dibenzoylpentane **6** (841.1 mg, 3.0 mmol) in 10 mL of HCl-saturated CH₂Cl₂ cooled in an ice bath was added powdered AlCl₃ (143 mg 1.07 mmol, 0.357 eq). After 5 min all AlCl₃ 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 (MgSO₄), passed through a short column of silica gel. After evaporation of the solution, the residue was separated by MPLC (SiO₂,

hexane-chloroform-EtOAc 3:1:0.25) to give **7** as colorless needles (681.5 mg, 86.6%), mp 107-108 °C (lit. ^{16b} mp 107-108 °C). ¹H NMR (270 MHz, CDCl₃) 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). ¹³C NMR (67.8 MHz, CDCl₃) 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.^{16b} for comparison purpose. Colorless plates (hexane-acetone), mp 79-80 °C (lit.^{6b} 78-79 °C). ¹H NMR (270 MHz, CDCl₃) 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). ¹³C NMR (67.8 MHz, CDCl₃) 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 CH₂Cl₂, To this solution was added TiCl₄ (150 μ L, 1.36 mmol, 0.45 eq) 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 quenched by addition of water. The product was extracted with chloroform. The extract was washed with water, dried (MgSO₄), filtered through a short column (SiO₂) and evaporated. The residue was separated by MPLC (SiO₂, 4:1:0.25 hexane-chloroform-EtOAc) to give **7** (31.8 mg, 4.0%), **9** (623 mg, 74.1%) as colorless plates (hexane-acetone), mp 127-128 °C (lit. ^{17a} mp 127-128 °C), and **6** (148 mg, 17.6%). ¹H NMR (270 MHz, CDCl₃) 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 D₂O exchange), 3.99 (dd, *J* = 11.9, 3.3 Hz, 1H), 2.15-1.78 (m, 5H), 1.78-1.38 (m, 3H). ¹³C NMR (67.8 MHz, CDCl₃) 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, a) Preparation of chalcone *II*. To a mixture of acetophenone (600 mg, 4.99 mmol), benzaldehyde (560 mg, 5.27 mmol) in 10 mL CH₂Cl₂ powdered AlCl₃ (360 mg, 2.70 mmol, 0.54 eq) was added. Considerable exothermic reaction occurred and a deep orange solution was resulted. After 2 h the reaction was quenched with water and extracted. The extract was washed with water, dried (MgSO₄), 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.

(b) *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 CH₂Cl₂ was added AlCl₃ (250 mg, 1.87 mmol, 0.374 eq) in an ice water bath. After 5 min 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 (MgSO₄), 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 acetophenone and benzaldehyde.

Aldol condensation of 1-phenylheptane-1,6-dione PhCO(CH₂)₄COMe. To a solution of 1-phenylheptane-1,6-dione (612.8 mg 3.0 mmol) in 10 mL of HCl-saturated CH₂Cl₂ was added AlCl₃ (138 mg, 1.03 mmol) at room temperature. After 5 min almost all AlCl₃

dissolved and a turbid pale tan solution was formed. After stirring for 5h, the reaction was quenched by addition of water and the product was extracted with chloroform. The extract was washed with water, dried (MgSO₄), filtered through a short column (SiO₂). 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 C₁₃H₁₄O: C, 83.83; H, 7.58. Found: C, 83.88; H, 7.46. ¹H NMR (270 MHz, CDCl₃) 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). ¹³C NMR (67.8 MHz, CDCl₃) δ 197.2, 150.0, 139.1, 136.1, 132.2, 128.8, 128.3, 40.4, 35.7, 22.1, 16.7.

A mixture of 1-phenyl-5-acetylcyclopentene 13 (R=Me) and 1-phenyl-2-acetyl-cyclopentene 14 (R=Me) (65:35 mixture by NMR): a colorless liquid (165 °C/1.0 mmHg), 411.3 mg (73.7%). Anal. Calcd. for C₁₃H₁₄O: C, 83.83; H, 7.58. Found C, 83.66; H, 7.53. ¹H NMR (270 MHz, CDCl₃) δ 7.42-7.18 (m, 5H), 6.43-6.38 (m, 0.65x1H), 4.05-3.96 (m, 0.65x1H), 2.92-2.76 (m, 0.65x2H), 2.73-2.56 (m, 0.65x2H), 2.47-2.23 (m, 0.35x2H), 2.17-2.05 (m,

0.35x2H), 2.03 (s, 0.65x3H), 1.96 (t, $J = 7.3$ Hz, 0.35x2H), 1.91 (s, 0.35x3H). ^{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 $\text{PhCO}(\text{CH}_2)_4\text{COEt}$. To a solution of 1-phenyloctane-1, 6-dione (218 mg, 1.0 mmol) in 3 mL of HCl sat 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** ($R = \text{Et}$) and major enone as a mixture of **13** and **14** ($R = \text{Et}$).

1-Ethyl-5-benzoylcyclopentene 15 ($R = \text{Et}$): a pale yellow liquid, 5.1 mg (2.5%) mixed with some other compounds which could not be removed due to the small sample amount. ^1H 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). ^{13}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.

A mixture of 1-phenyl-5-propanoylcyclopentene 13 (R=Et) and

1-phenyl-2-propanoyl-cyclopentene 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 C₁₄H₁₆O:

C, 83.96; H, 8.05. Found: C, 83.63; H, 8.06. EI Mass Calcd. 200.12. Found 200.10. ¹H

NMR (270 MHz, CDCl₃) δ 7.40-7.16 (m, 5H), 6.40-6.35 (m, 0.80 x 1H), 4.08-3.99 (m, 0.80

x 1H), 2.90-1.91 (m, 0.20 x 8H + 0.80 x 6H), 0.93 (t, *J* = 7.2 Hz, 0.80 x 3H), 0.91 (t, *J* = 7.2

Hz, 0.20 x 3H). ¹³C NMR (67.8 MHz, CDCl₃) 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-benzoylcyclopentanone 17. A solution of **2** (100

mg) in 2 mL benzene was exposed to sun light. 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. ^{19a} mp 159-159.5 °C).

¹H NMR (270 MHz, CDCl₃) 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). ¹³C NMR (67.8 MHz, CDCl₃) 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 ¹H and ¹³C NMR spectra, the coordinates and energies of the calculated structures of **2-5**, and **9**, and the X-ray structure files (cif) for **4** and **17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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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 $\text{C}_{19}\text{H}_{18}\text{O}$ in low yield. Kipping, S.; Perkin Jr., W. H. *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).

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(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. L. Claisen, A. Claparede, *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 Jr., S. H.; 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.