

The reaction of ketones with benzaldehyde catalyzed by $\text{TiCl}_4 \cdot 2\text{THF}$

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Abstract

In the presence of a catalytic amount of $\text{TiCl}_4 \cdot 2\text{THF}$, chosen ketones reacted with benzaldehyde to give different kinds of condensation products in satisfactory yields under mild conditions.

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1. Introduction

Titanium chemistry offers great advantages in organic synthesis because titanium derivatives are cheap and non-toxic [1]. It is well known that titanium(IV) chloride is widely used in many reactions [2]. There are examples of the coupling of carbonyl compounds [3], aldol condensations [4], Michael additions [5], Friedel–Crafts reactions [6] and conversion of propargylic alcohols to α,β -acetylenic aldehydes [7], alkyl azides and ketones to amides [8], acetals and ketals to carbonyl compounds [9] and so on. In these reactions, TiCl_4 is employed stoichiometrically. There are also reports on the use of catalytic amount of TiCl_4 in Baylis–Hillman reactions [10], pinacol coupling reactions [11], Diels–Alder reactions [12] and Claisen rearrangement [13], etc.

Now, we report the study on the reactions of ketones with benzaldehyde using a catalytic amount of $\text{TiCl}_4 \cdot 2\text{THF}$ under mild condition.

2. Experimental

All reactions were carried out under an atmosphere of dry argon using the standard Schlenk techniques. $\text{TiCl}_4 \cdot 2\text{THF}$ was prepared by literature procedure [14]. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker ORX-500 MHz spectrometer with TMS as an internal standard in CDCl_3 . IR spectra were recorded on a Nicolet Magna-550 spectrometer. Mass spectra were obtained on a HP5989A spectrometer. Melting points were obtained in open capillary tubes and uncorrected.

2.1. *Trans*-1,3-diphenyl-2-propen-1-one (2)

To a mixture of acetophenone (**1a**) (6.12 g, 51.0 mmol) and benzaldehyde (15.6 mL, 153 mmol) in a Schlenk flask was added $\text{TiCl}_4 \cdot 2\text{THF}$ (1.70 g, 5.10 mmol) with stirring. The reaction was carried out at 120 °C for 16 h under argon and then quenched with 20 mL H_2O . The superfluous benzaldehyde was removed by steam distillation and then could be reclaimed. The rest mixture was extracted with CH_2Cl_2 (20 mL \times 3). The organic phase was washed with saturated aqueous Na_2CO_3 solution and brine, dried over MgSO_4 and the solvent was removed under vacuum. The residue was purified by recrystallization from petroleum ether to give a pale yellow crystal: *trans*-1,3-diphenyl-2-propen-1-one (**2**).

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Yield: 9.40 g, 86.2%; mp 54–56 °C (Ref. [15] mp 53–55 °C); ¹H NMR (500 MHz, CDCl₃) δ: 7.57 (d, *J* = 15.8 Hz, 1H), 7.82 (d, *J* = 15.8 Hz, 1H), 7.43–8.02 (m, 10H).

2.2. 2,5-Di(benzylidene)cyclopentanone (3)

The reaction was run at 120 °C for 4 h starting from cyclopentanone (**1b**) (3.65 g, 43.5 mmol) benzaldehyde (13.3 mL, 130 mmol) and TiCl₄·2THF (1.45 g, 4.34 mmol). The residue was recrystallized from ethyl acetate to give 2,5-di(benzylidene)cyclopentanone (**3**). Yield: 9.80 g, 86.7%; mp 187–190 °C (Ref. [16] mp 190–191 °C); ¹H NMR (500 MHz, CDCl₃) δ: 3.14 (s, 4H), 7.39–7.61 (m, 12H).

2.3. 2,6-Di(benzylidene)cyclohexanone (4)

According to the procedure described in Section 2.1, starting from cyclohexanone (**1c**) (2.84 g, 29.0 mmol) benzaldehyde (8.9 mL, 87.3 mmol) and TiCl₄·2THF (0.97 g, 2.90 mmol), the residue was recrystallized from ethyl acetate to give 2,6-di(benzylidene)cyclohexanone (**4**). Yield: 5.92 g, 75.0%; mp 116–118 °C (Ref. [16] mp 118–118.5 °C); ¹H NMR (500 MHz, CDCl₃) δ: 1.78 (m, 2H), 2.93 (t, *J* = 6.2 Hz, 4H), 7.30–7.45 (m, 10H), 7.80 (s, 2H).

2.4. 2,5-Dimethyl-3,4-diphenyl-2-cyclopenten-1-one (5)

According to the procedure described in Section 2.1, starting from 3-pentanone (**1d**) (17.2 g, 200 mmol) benzaldehyde (61.3 mL, 601 mmol) and TiCl₄·2THF (6.69 g, 20.3 mmol), the residue was recrystallized from ethanol to give 2,5-dimethyl-3,4-diphenyl-2-cyclopenten-1-one (**5**). Yield: 42.1 g, 80.1%; mp 117–119 °C (Ref. [17] mp 116–117 °C); ¹H NMR (500 MHz, CDCl₃) δ: 1.34 (d, *J* = 7.3 Hz, 3H), 2.02 (s, 3H), 2.40 (m, 1H), 3.97 (m, 1H), 7.05–7.35 (m, 10H).

2.5. 2,3,4,5-Tetraphenyl-2-cyclopenten-1-one (6)

According to the procedure described in Section 2.1, starting from 1,3-diphenylacetone (**1e**) (3.68 g, 17.5 mmol) benzaldehyde (5.4 mL, 53.0 mmol) and TiCl₄·2THF (0.58 g, 1.75 mmol), the reaction was carried out at 120 °C for 16 h. The residue was recrystallized from methanol to give 2,3,4,5-tetraphenyl-2-cyclopenten-1-one (**6**). Yield: 5.00 g, 80.2%; mp 160–163 °C (Ref. [17] mp 162–163 °C); ¹H NMR (500 MHz, CDCl₃) δ: 3.75 (d, *J* = 2.4 Hz, 1H), 4.56 (d, *J* = 2.4 Hz, 1H), 7.13–7.36 (m, 20H).

2.6. 2,5-Diethyl-3,4-diphenyl-2-cyclopenten-1-one (7) and 1-phenyl-2-ethyl-1-hexen-3-one (8)

According to the procedure described in Section 2.1, starting from 4-heptanone (**1f**) (15.5 g, 136 mmol) benzaldehyde (41.6 mL, 408 mmol) and TiCl₄·2THF (4.55 g, 13.6 mmol), the reaction was carried out at 120 °C for 16 h. The reac-

tion mixture was distilled to give 1-phenyl-2-ethyl-1-hexen-3-one (**8**). Yield: 7.56 g, 19.0%; bp 90–94 °C/133 Pa; ¹H NMR (500 MHz, CDCl₃) δ: 0.90 (t, *J* = 7.4 Hz, 3H), 1.02 (t, *J* = 7.4 Hz, 3H), 1.64 (m, 2H), 2.45 (q, *J* = 7.4 Hz, 2H), 2.68 (t, *J* = 7.4 Hz, 2H), 7.24–7.33 (m, 5H), 7.37 (s, 1H); ¹³C NMR (500 MHz, CDCl₃) δ: 14.37, 14.47, 19.00, 20.40, 40.38, 128.95, 129.09, 129.75, 136.51, 138.46, 144.53, 202.98; IR (film): 700, 1200, 1630, 1670 cm⁻¹; HRMS (*m/z*): Calcd. For C₁₄H₁₈O: 202.1358. Found: 202.1361. And then the residue was recrystallized from ether to give 2,5-diethyl-3,4-diphenyl-2-cyclopenten-1-one (**7**). Yield: 18.6 g, 47.0%; mp 89–91 °C (Ref. [17] mp 92–93 °C); ¹H NMR (500 MHz, CDCl₃) δ: 1.03 (t, *J* = 7.5 Hz, 3H), 1.15 (t, *J* = 7.5 Hz, 3H), 1.70 (m, 1H), 1.93 (m, 1H), 2.40 (m, 3H), 4.05 (s, 1H), 7.05–7.30 (m, 10H).

2.7. 5-Benzylidene-3,4-diphenyl-2-methyl-2-cyclopenten-1-one (9)

According to the procedure described in Section 2.1, starting from butanone (**1g**) (3.60 g, 50.0 mmol) benzaldehyde (15.3 mL, 150 mmol) and TiCl₄·2THF (1.67 g, 5.00 mmol). The residue was recrystallized from methanol to give 5-benzylidene-3,4-diphenyl-2-methyl-2-cyclopenten-1-one (**9**). Yield: 11.3 g, 65.6%; mp 150–152 °C; ¹H NMR (500 MHz, CDCl₃) δ: 2.02 (d, *J* = 1.5 Hz, 3H), 5.16 (d, *J* = 1.5 Hz, 1H), 7.03–7.60 (m, 16H); ¹³C NMR (500 MHz, CDCl₃) δ: 10.60, 52.38, 127.43, 128.64, 128.94, 128.98, 129.51, 129.81, 130.27, 131.51, 132.69, 135.03, 135.52, 138.05, 138.33, 139.68, 167.02, 198.51; IR (KBr): 705, 1350, 1620, 1640, 1680 cm⁻¹; HRMS (*m/z*): Calcd. For C₂₅H₂₀O: 336.1514. Found: 336.1479.

3. Results and discussion

3.1. The effect of the amount of TiCl₄·2THF

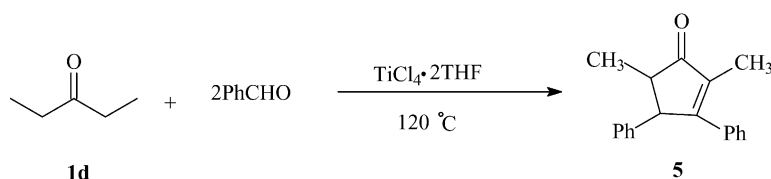
Heating the mixture of 3-pentanone (**1d**), benzaldehyde and the catalyst at 120 °C for 16 h, the cyclocondensation product 2,5-dimethyl-3,4-diphenyl-2-cyclopenten-1-one (**5**) was mainly obtained (Scheme 1).

The results of the set of experiments carried out with different amount of TiCl₄·2THF are summarized in Table 1. As can be seen, increase in the amount of TiCl₄·2THF from 2 to

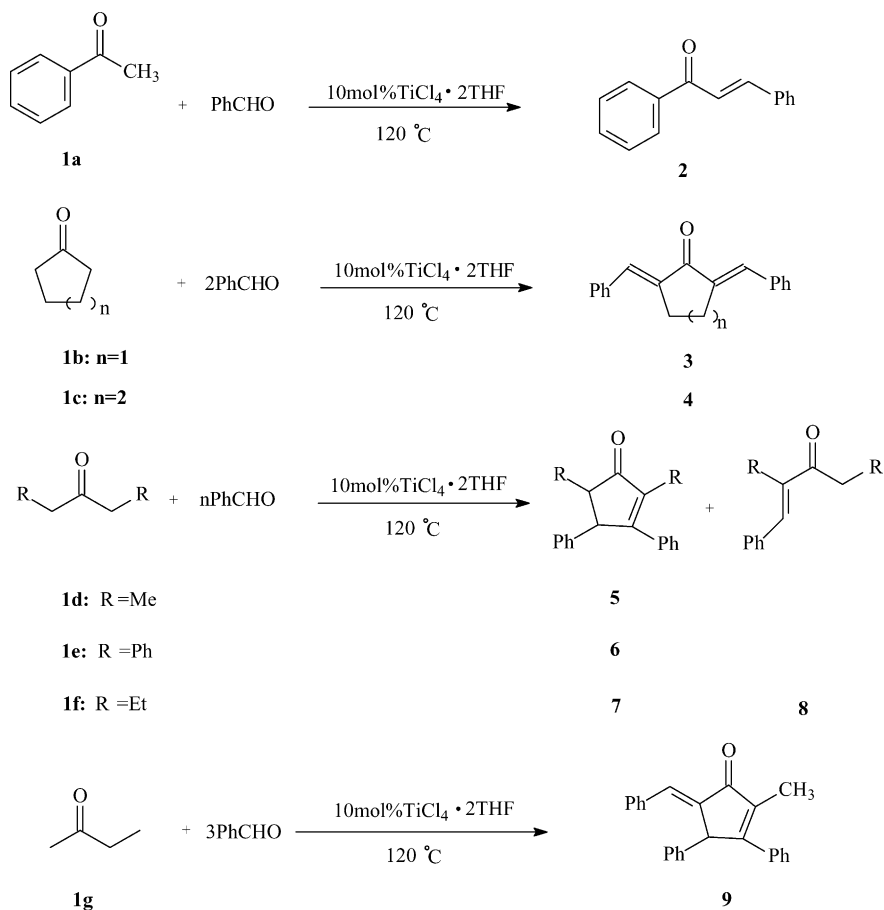
Table 1
The effect of the amount of the catalyst

Entry	TiCl ₄ ·2THF (mol%)	Yield (%)
1	2	45.0
2	5	56.5
3	10	80.1
4	20	81.4
5	50	82.5

Reaction conditions: molar ratio of 3-pentanone:benzaldehyde = 1:3, 120 °C, 16 h.



Scheme 1.



Scheme 2.

10 mol% equivalent greatly increased the yield of the product. But further increase in the amount of $\text{TiCl}_4 \cdot 2\text{THF}$ did not increase the yield significantly. So 10 mol% of the catalyst as the optimum amount was chosen in this reaction.

3.2. The reactions of different kinds of ketones with benzaldehyde catalyzed by $\text{TiCl}_4 \cdot 2\text{THF}$

We studied the reactions of ketones with benzaldehyde catalyzed by 10 mol% $\text{TiCl}_4 \cdot 2\text{THF}$ (Scheme 2). The results are presented in Table 2.

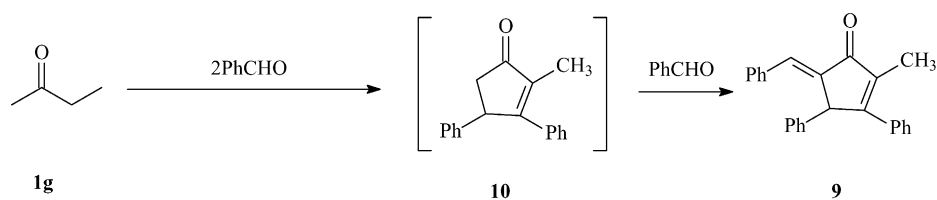
The condensation of acetophenone (**1a**) with benzaldehyde gave (*E*)-chalcone (*trans*-1,3-diphenyl-2-propen-1-one) (**2**). Cyclic ketones such as cyclopentanone (**1b**) and cyclohexanone (**1c**) gave 2,5-di(benzylidene)cyclopentanone

Table 2
The reactions of ketones and benzaldehyde catalyzed by $\text{TiCl}_4 \cdot 2\text{THF}$

Entry	Ketone	Product	Yield (%)
1	1a	2	86.2
2 ^a	1b	3	86.7
3	1c	4	75.0
4	1d	5	80.1
5	1e	6	80.2
6	1f	7	47.0
		8	19.0
7	1g	9	65.6

Reaction conditions: molar ratio of ketone:benzaldehyde: $\text{TiCl}_4 \cdot 2\text{THF}$ = 1:3:0.1, 120 °C, 16 h.

^a Reaction time was 4 h.



Scheme 3.

(**3**) and 2,6-di(benzylidene)cyclohexanone (**4**), respectively. These α,β -unsaturated ketones are important intermediates in the synthesis of the heterocyclic compounds [18]. Our method may provide a useful route for their preparation [16,19]. It is generally accepted that $\text{TiCl}_4 \cdot 2\text{THF}$, as a strong Lewis acid, complexes with the ketones and benzaldehyde and then forms the titanium enolate [20]. The benzaldehyde carbonyl group is activated for the nucleophilic addition by complexation with TiCl_4 [20].

It is interesting to note that when acyclic ketones were used, polysubstituted cyclopentenones could be isolated in satisfactory yields. The condensation of 3-pentanone (**1d**) or diphenylacetone (**1e**) with benzaldehyde gave 2,5-dimethyl-3,4-diphenyl-2-cyclopenten-1-one (**5**) or 2,3,4,5-tetraphenyl-2-cyclopenten-1-one (**6**), respectively. It was easy to obtain these recrystallized products from alcohol in high yields after an excess amount of benzaldehyde was removed by steam distillation. Similarly, the reaction of 4-heptanone (**1f**) with benzaldehyde produced 2,5-diethyl-3,4-diphenyl-2-cyclopenten-1-one (**7**) in a comparatively lower yield together with a small amount of 1-phenyl-2-ethyl-1-hexen-3-one (**8**). During further study of the reaction conditions, we found that **8** always existed and when using it to react with benzaldehyde under the conditions described in Section 2.1 2,5-diethyl-3,4-diphenyl-2-cyclopenten-1-one (**7**) was obtained as expected. The activity with the variation of substituted group on the ketone decreases as follows: $\text{Ph} \sim \text{Me} > \text{Et}$, which is similar to the activity of the enolization [21]. The reaction may involve the double aldol cross-condensation of the ketones and the Nazarov cyclization [22] of the resulting condensates in one pot [13]. Butanone (**1g**), a methyl ketone, reacted with 3 equiv of benzaldehyde to form 5-benzylidene-3,4-diphenyl-2-methylcyclopenten-1-one (**9**), which was possibly formed by the way of the intermediate (**10**) [17] (Scheme 3).

Polysubstituted cyclopentenones are not only perfume chemicals and pharmaceutical intermediates but also important precursors for polysubstituted cyclopentadienes which are versatile ligands of various organometallic complexes [23]. There are many reports on the synthesis for polysubstituted cyclopentenones, but the preparation is generally troublesome and requires a multistep synthesis [24]. In 1993, Yuki et al. reported a one-pot synthesis of polysubstituted cyclopentenones through the reactions of acyclic ketones with aldehydes catalyzed by the zirconium derivatives at 130–200 °C in a sealed tube [17].

Here we have developed a simple and general method for the synthesis of polysubstituted cyclopentenones using the inexpensive and easily available $\text{TiCl}_4 \cdot 2\text{THF}$ as catalyst. The method offered several advantages including high yields and a simple experimental workup procedure, which made it a useful process for the synthesis of polysubstituted cyclopentenones.

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