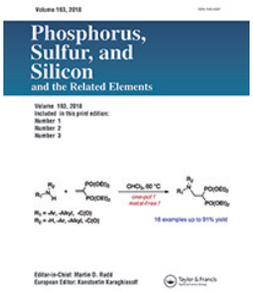

Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: 1042-6507 (Print) 1563-5325 (Online) Journal homepage: http://www.tandfonline.com/loi/gpss20

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To cite this article: Yunxia Yang, Le Wang, Yuan Chen, Yiru Dai & Zhihua Sun (2018) One-pot synthesis of α,α-disubstituted Aryl-1-ethanones via the Wittig-Horner reaction, Phosphorus, Sulfur, and Silicon and the Related Elements, 193:3, 121-126, DOI: 10.1080/10426507.2017.1415899

To link to this article: https://doi.org/10.1080/10426507.2017.1415899

PHOSPHORUS, SULFUR, AND SILICON
2018, VOL. 193, NO. 3, 121–126
https://doi.org/10.1080/10426507.2017.1415899

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One-pot synthesis of α,α-disubstituted Aryl-1-ethanones *via* the Wittig-Horner reaction

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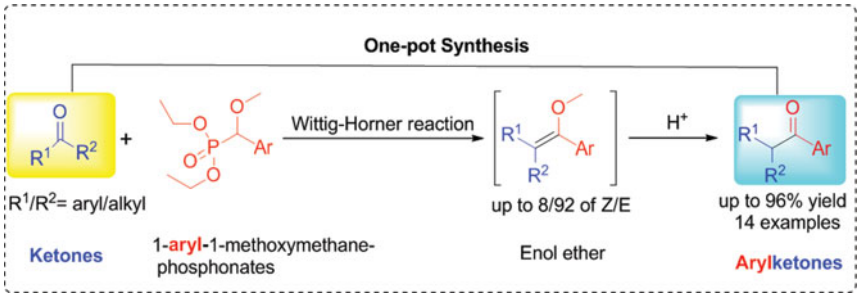
ABSTRACT

A one-pot methodology for the synthesis of α,α-disubstituted aryl-1-ethanones *via* the Wittig-Horner reaction has been developed and described in this manuscript. Both aryl/alkyl and dialkyl α-branched arylethanone were obtained in high yields (up to 96%) without the use of any metal catalysts. A total of 14 α,α-disubstituted arylethanone derivatives were synthesized based on this simple method that easily converts the carbonyl carbon (sp^2) into the sp^3 carbon. This versatile method is expected to further promote the use of substituted ketones as synthetic building blocks to construct a variety of α-branched aryl ketones.

ARTICLE HISTORY
Received 3 September 2017
Accepted 8 November 2017

KEYWORDS
α,α-disubstituted aryl-1-ethanones; active phosphonates; one-pot synthesis; Wittig-Horner reaction

GRAPHICAL ABSTRACT



Introduction

Aryl ketone moieties are widely found in drugs and medicinal intermediates due to their extraordinary biological and pharmaceutical properties.[1–8] For example, pitofenone and n-butylphthalide (NBP) are well-known antiplatelet and antispasmodic drugs in the market.[9] Moreover, aryl ketone derivatives are also pivotal structural motifs in many biologically active natural products.[10–13] Therefore, it is very important to develop different efficient protocols to construct aryl carbonyl compounds.

Among various effective methods for the synthesis of ketones, the Friedel-Crafts acylation[14,15] and transition-metal catalyzed acylation[16–20] are the most common methods (Scheme 1a). Although these protocols are effective in forming arylketones, the synthesis of branched arylketones remains challenging, and documented examples are rather limited so far,[21–23] with three elegant examples shown in Scheme 1b.[24–27] Despite the fact that branched arylketones could be derived from these ketones, the carbonyl group (sp^2) of the ketone moiety usually does not change, which is not very convenient to construct branched arylketones. Herein, we demonstrate a one-pot synthesis of α-branched arylketones based on the Wittig-Horner reaction (Scheme 1c). The carbonyl (sp^2) moiety of ketones are successfully converted into the sp^3 carbon to afford α,α-branched arylketones. Substituted ketones are versatile building blocks to construct versatile α-branched aryl ketones. The well-known Wittig-Horner reaction is widely used in the synthesis of alkenes with active phosphonates and aldehydes as the building blocks. However, the suitability of ketones is limited because of the apparent steric effect.[28–31] The resulting enol ethers can be readily converted to branched arylketones in an acid medium.[32] Since there were quite few examples of such enolethers to form ketone in the literature,[33–34] we were prompted to develop a systemic and extensive research to construct a serious of α-branched arylketones *via* the Wittig-Horner reaction. This manuscript describes the synthesis of a series of α-branched (aryl/alkyl and dialkyl) arylketones in high yields under relatively mild conditions in

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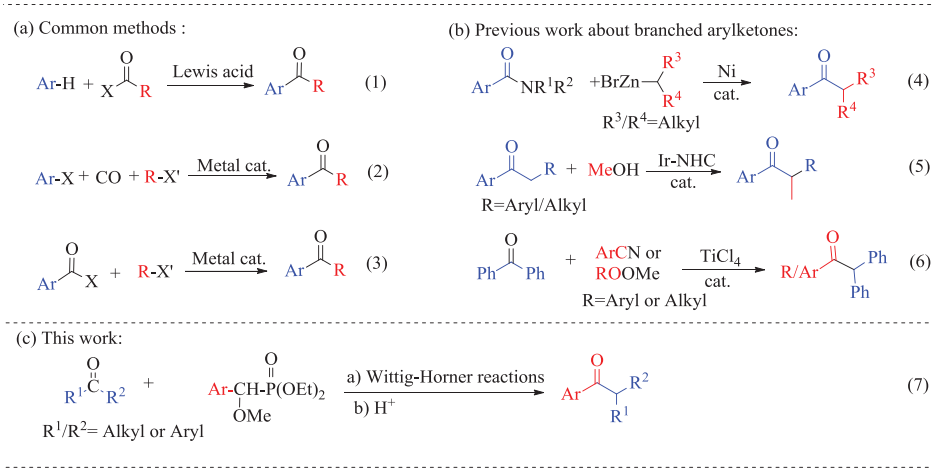


Scheme 1. The synthesis of arylketones.

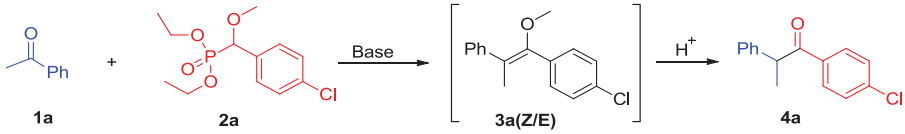
one step. Moreover, the strategy described herein also provides a very versatile way to synthesize a variety of α-branched arylketones, with substituted ketones as starting materials.

Results and discussion

Acetophenone (1a) and diethyl 1-(*p*-chlorophenyl)-1-methoxymethanephosphonate (2a) were used as model compounds to optimize the reaction conditions (Table 1). Different conditions, such as the base used, the reaction time, and the temperature, were explored to optimize the synthesis as listed in Table 1. The synthesis of the phosphonates followed the literature reports[35–37] and the details are shown in the Supporting Information. It is evident from the data presented in Table 1 that *t*-BuONa and *n*-BuLi produced higher yields of 4a compared to other bases (e.g. $NaNH_2$ and K_2CO_3). When *t*-BuONa was used as the base, the α,α-disubstituted aryl-1-ethanone 4a could be obtained under mild conditions with up to 88% yield (entry 5), and various yields by altering the temperature and reaction time (entries 3–5). The yield of **4a** was further improved to 93% with the much stronger base *n*-BuLi at −78°C, and the stereo selectivity of **3a** was significantly improved, with an *E*/*Z* (**3a**) ratio even up to 92:8 (entry 6). Obviously, a higher selectivity is obtained at lower temperatures (entries 6–8). Considering that the H_2SO_4 was too harsh an acid herein, other acids were used to explore their catalytic efficiency. We found hydrolysis completed by the use of citric acid or trifluoroacetic acid (TFA). Considering the previous reports of protonation of enols,[34] the reaction was modified and performed with *n*-BuLi at −78°C in THF and subsequent hydrolysis by TFA. While the configuration of the intermediate **3a** does not affect the final product, it is important to further confirm its stereochemistry. **3a** was isolated and characterized with respect to the *E*/*Z* ratio. Moreover, 1D selective NOE (Nuclear Overhauser Effect)[38,39] experiment were also used to confirm the *E* configuration of **3a**. A representative 1D selective NOE spectrum is shown in Fig. S4. (See Supporting Information). Irradiation of the CH_3 protons resulted in clear NOE of the OCH_3 protons, indicating that they are in close proximity and thus the *E*-alkenes was formed.

After establishing the optimal reaction conditions (Table 1, entry 6), different aryl/alkyl ketones (**1a-g**) were used to test this method. (Table 2). As we expected, most of the target compounds were obtained in high yields (90–96%) *via* hydrolysis without isolating the intermediate compounds **3**. Some

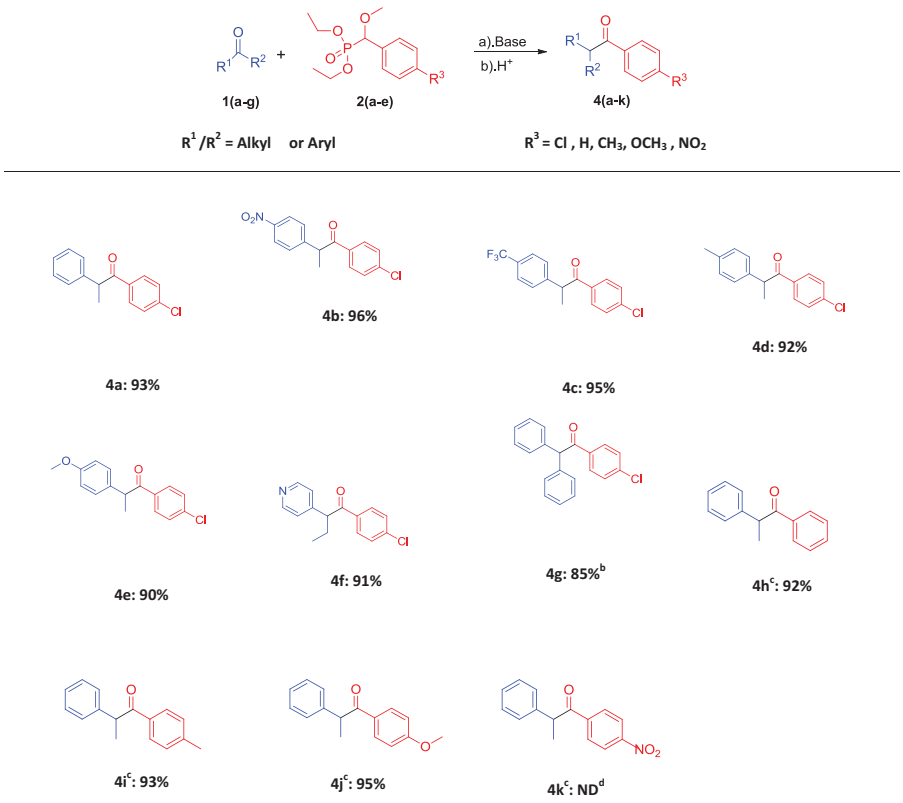
Table 1. Optimization of reaction conditions[a].



Entry	Base	Solvents	Temp. (°C)	Time (h)	Ratio of **3a** Z/E[c] (%)	Yield of **4a**[e] (%)
1	$NaNH_2$	C_6H_6	80	12	ND[d]	<10
2	K_2CO_3	DMF	80	12	ND[d]	<10
3	*t*-BuONa	DMF	r.t.	24	ND[d]	50
4	*t*-BuONa	DMF	80	12	48:52	83
5	*t*-BuONa	DMF	50	24	45:55	88
6	*n*-BuLi	THF	−78	3[b]	8:92	93
7	*n*-BuLi	THF	−20	3[b]	31:69	74
8	*n*-BuLi	THF	0	3[b]	ND[d]	45

[a]General procedure: The base was added dropwise to the diethyl phosphonate dissolved in the relevant solvent at the temperature mentioned. After reacting with acetophenone, the reaction mixture was hydrolyzed by 37% H_2SO_4, r.t., 2 h; [b] −78 / −20/0°C, 0.5 h.; r.t., 2.5 h.; [c]Determined by ^{1}H NMR and NOE; [d]Not determined; [e]The crude yield of **4a** was determined by LC-MS.

Table 2. Synthesis of α,α-aryl/alkylaryl-1-ethanone (**4a-k**)[a].

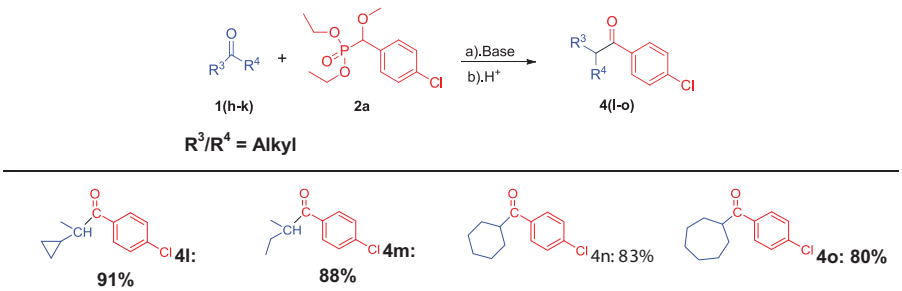


[a]Reaction conditions: *n*-BuLi (1.1 equiv.), phosphonate (1.0 equiv.), ketone (1.5 equiv.), THF, −78°C, 3 h.; TFA, r.t.,12 h. [b]The hydrolysis time was 12 h. [c]Diethyl phosphate; [d]Not determined.

alkenes intermediates were isolated and characterized with respect to the ratio of E/Z, while it seems that the one-pot methodology for the synthesis of α,α-disubstituted arylketones is more effective. With the same phosphonate **2a**, *p*-nitro- and *p*-trifluoromethyl arylketones provided excellent yields (95–96%, **4b-c**), which indicates that electron withdrawing groups increase the activity of arylketones. As pyridine is an electron-poor arene, substrate **1f** also provided high yield of **4f** (91%). For a substrate with steric hindrance, the yield of 1,2,2-triaryl-1-ethanone **4g** is slightly reduced to 85%. Meanwhile, other 1-aryl-1-alkoxy-methanephosphonates (**2a-e**) with different groups were also investigated. As shown in Table 2, the phosphonates **2a-d** with electron donating groups and weak electron withdrawing groups, such as methyl, methoxy, chorine, can provided excellent yields (92–95%) of **4a,4h-j**. However, *p*-nitrophenylphosphonate **2e** does not effectively react, perhaps because the strong electron withdrawing effect deactivates the phosphonate.[28]

To further check the applicability of the strategy, the reaction was carried out with dialkylketones under optimal conditions. Four symmetric and asymmetric alkylketones (**1h-k**) were selected and investigated. As shown in Table 3, four α,α-dialkyl-aryl-aryl-1-ethanones were obtained in high yields (80–91%). Especially, asymmetric dialkyl arylketones (**4l-m**) were obtained in the higher yields (88–91%), while similar ketones were only obtained in low or moderated yields (e.g. 62–72%) by the use of metal catalyst, as described in previous work.[26] These studies further expanded the scope of substrate ketones, which illustrates that both arylketones and alkylketones can provide branched arylketones through this method.

Table 3. Synthesis of α,α-diarylaryl-1-ethanones from dialkylketones **1h-k**[a].



[a]Reaction conditions: *n*-BuLi (1.1 equiv.), phosphonate (1.0 equiv.), ketone (1.5 equiv.), THF, −78°C,3 h.; TFA, r.t.,12 h.

Conclusion

In summary, we have developed a very convenient one-pot method for the synthesis of α-branched arylketones *via* the Wittig-Horner reaction from simple ketones, in which both α,α-aryl/alkyl and dialkyl aryl-1-ethanone were obtained in high yields (>90%) under various, mostly mild conditions. Therein the carbonyl (sp^2) moiety of ketones is successfully converted into the sp^3 carbon to afford various α-branched aryl ketones. We believe that the strategy presented in this work will be useful in the field of synthetic medicinal chemistry.

Experimental

Chemicals and apparatus

The solvents were dried as follows. THF was heated at reflux over sodium benzophenone ketyl. NMR spectra were recorded in $CDCl_3$ with a Bruker Advance II spectrometer at 400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F, 162 MHz for ^{31}P. Chemical shifts are given in parts per million. LC-MS (ESI) analyses was carried out with an Agilent 1100 LC/MSD. The Supplemental Materials contains sample 1H and 13C NMR spectra of the products (Figures S 1 – S 37).

General procedure for the preparation of α,α-disubstituted aryl-1-ethanones

n-BuLi (1.1 equiv., 3.3 mmol) was added dropwise to a solution of 3 mmol of phosphonate **2** in THF (10 mL) at −78°C. The mixture was kept at this temperature for 10 min. Then ketone **1** (1.5 equiv., 4.5 mmol) was added. The resulting mixture was stirred for 30 min at −78°C, allowed to warm up to r.t. for 2.5 h followed by addition of saturated NH_4Cl-H_2O solution (5 mL); and extracted with EtOAc (3 × 10 mL). The organic phases were dried and hydrolyzed by TFA (5 mL, r.t., 12 h), the extracted liquid was subjected to flash chromatography to isolate the desired products which were characterized with NMR and LC-MS. If the organic phase was purified directly by column chromatography without further hydrolysis, the intermediate **3**-*E was* obtained.

(E)-4-(1-Methoxy-2-phenylpropene-1-yl)chlorobenzene (3a-E)

Yellow oil. ^{1}H NMR: δ 7.13–7.18 (m, 5H, Ar*H*), 7.06 (d, J = 8.8 Hz, 4H, ClAr*H*), 3.45 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3). 1D-NOE: Irradiation of 2.20 (s, CH_3) found: 7.06 (m, ClAr*H*), 3.45 (s, OCH_3). MS: calcd. $C_{16}H_{15}ClO$: *m/z* 258.08; found: 259.1 $[M+H]^+$.

1-(4-Chlorophenyl)-2-phenyl-1-propanone (4a)

Yellow oil. ^{1}H NMR: δ 7.90 (d, J = 8.8 Hz, 2H, ClAr*H*), 7.30–7.37 (m, 7H, ClAr*H,* Ar*H*), 4.62–4.64 (m, 1H, C*H*), 1.55 (d, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR: δ 199.1, 141.4, 139.2, 134.8, 130.2, 129.1, 128.8, 127.7, 127.1, 48.1, 19.4. MS: calcd. $C_{15}H_{13}ClO$ *m/z* 244.07; found 245.1 $[M+H]^+$.

1-(4-Chlorophenyl)-2-(4-nitrophenyl)-1-propanone (4b)

Yellow oil. ^{1}H NMR: δ 7.27 (m, 1H), 8.19 (d, J = 8.8 Hz, 2H, NO_2-Ar*H*), 7.88 (d, J = 8.4 Hz, 2H, ClAr*H*), 7.47 (d, J = 8.8 Hz, 2H, NO_2-Ar*H*), 7.41 (d, J = 8.8 Hz, 2H, ClAr*H*), 4.78–4.79 (m, 1H, C*H*), 1.59 (d, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR: δ 197.9, 148.3, 147.1, 139.9, 134.2, 130.1, 129.1, 128.7, 124.6, 47.6, 19.3. MS: calcd. $C_{15}H_{12}ClNO_3$ *m/z* 289.05.; found 290.1 $[M+H]^+$.

1-(4-Chlorophenyl)-2-(4-trifluoromethylphenyl)-1-propanone(4c)

Yellow oil. ^{1}H NMR: δ 7.89 (d, J = 8.8 Hz, 2H, ClAr*H*), 7.58 (d, J = 8.0 Hz, 2H, ClAr*H*),7.40–7.42 (m,4H, CF_3-Ar*H*), 4.70–4.75 (m, 1H, C*H*), 1.57 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR: δ 198.3, 139.7, 134.4, 130.1, 129.3, 128.9, 128.1, 126.1, 126.0, 125.9, 125.9, 47.7, 19.3. ^{19}F NMR: −62.6. MS: calcd. $C_{16}H_{12}ClF_3O$ *m/z* 312.05.; found 313.0 $[M+H]^+$.

1-(4-Chlorophenyl)-2-(p-tolyl)-1-propanone (4d)

Yellow oil. ^{1}H NMR: δ 7.90 (d, J = 8.4 Hz, 2H, ClArH), 7.37 (d, J = 8.8 Hz, 2H, CH_3Ar*H*), 7.146 (m, 4H, ClAr*H*, CH_3-Ar*H*), 4.59–4.61 (m, 1H, C*H*), 2.31 (s, 3H, ArCH_3), 1.53 (d, J = 6.8 Hz, 3H, CHCH_3). ^{13}C NMR: δ 199.2, 139.1, 138.2, 136.7, 134.9, 130.2, 129.8, 128.8, 127.6, 47.7, 20.9, 19.4. MS: calcd. $C_{16}H_{15}ClO$: *m/z* 258.08.; found 259.1 $[M+H]^+$.

1-(4-Chlorophenyl)-2-(4-methoxyphenyl)-1-propanone (4e)

Yellow oil. ^{1}H NMR: δ 7.89 (d, J = 8.8 Hz, 2H, ClAr*H*), 7.36 (d, J = 8.4 Hz, 2H, ClAr*H*), 7.19 (d, J = 8.8 Hz, 2H, CH_3O-Ar*H*), 6.85 (d, J = 8.8 Hz, 2H, CH_3O-Ar*H*), 4.58–4.60 (m,1H, C*H*), 3.78 (s, 3H, OCH_3), 1.52 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR: δ 199.3, 158.6, 139.1, 134.9, 133.2, 130.1, 128.7, 114.5, 55.2, 47.2, 19.4. MS: calcd.$C_{16}H_{15}ClO_2$: *m/z* 274.08.; found 275.2 $[M+H]^+$.

1-(4-Chlorophenyl)-2-(pyridinyl-3-yl)-1-butanone (4f)

Yellow oil. ^{1}H NMR: δ 8.61(s,1H, NC*H*), 8.51(s,1H, NC*H*), 7.91 (d, J = 8.4Hz, 2H, ClAr*H*), 7.66 (d, J = 8.0 Hz, 1H, NCH-CH-*CH*), 7.41 (d, J = 8.8 Hz, 2H, ClAr*H*), 7.26–7.28 (m, 1H, NCH-*CH*), 4.46(t, J = 7.2 Hz, 1H, C*H*), 2.18–2.29 (m, 1H, CH_2), 1.84–1.93 (m, 1H, CH_2), 0.92–0.96 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR: δ 198.20, 148.56, 139.79, 135.48, 135.02, 134.81, 129.96, 129.05, 123.92, 77.31, 76.99, 76.67, 52.43, 27.13, 12.12. MS: calcd. $C_{15}H_{14}ClNO$: *m/z* 259.08; found 260.2 $[M+H]^+$.

1-(4-Chlorophenyl)-2,2-diphenyl-1-ethanone (4g)

Yellow solid, m.p. 106–105°C. ^{1}H NMR: δ 7.95 (d, J = 8.6 Hz, 2H, Ar*H*), 7.83 (d, J = 7.2 Hz, 2H, Ar*H*), 7.61 (t, J = 7.4 Hz, 1H, Ar*H*), 7.51 (t, J = 7.6 Hz, 2H, Ar*H*) 7.39 (d, J = 8.6 Hz, 2H, Ar*H*), 7.33–7.35 (m, 3H, Ar*H*), 7.26–7.28 (m, 2H, Ar*H*), 5.99 (s, 1H, C*H*). ^{13}C NMR: δ 196.9, 139.5, 138.8, 137.7, 135.1, 132.4, 130.4, 130.0, 129.1, 128.9, 128.8, 128.3, 127.3, 59.6. MS: calcd. $C_{20}H_{15}ClO$: *m/z* 306.08; found 307.1 $[M+H]^+$.

1,2-Diphenyl-1-propanone (4h)

Yellow solid, m.p.: 78.4–79.7°C. ^{1}H NMR: δ 7.98 (d, J = 10 Hz, 2H, CO-Ar*H*), 7.50–7.52 (m, 1H, CO-Ar*H*), 7.39–7.42 (m, 2H, CO-Ar*H*), 7.28–7.38 (m, 4H, CH-*ArH*), 7.21–7.24 (m, 1H, CH-*ArH*), 4.71–4.73 (m, 1H, C*H*), 1.56 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR: δ 200.3, 141.5, 136.5, 132.8, 129.5, 128.9, 128.8, 128.5, 127.8, 126.9, 47.9, 19.5. MS: calcd. $C_{15}H_{14}O$: *m/z* 210.10.; found 211.1 $[M+H]^+$.

2-Phenyl-1-(p-tolyl)-1-propanone (4i)

Yellow oil. ^{1}H NMR: δ 7.88 (d, J = 8.0 Hz, 2H, CO-Ar*H*), 7.28–7.31 (m, 5H, CH-Ar*H*), 7.20 (d, J = 8.0 Hz, 2H, CO-Ar*H*), 4.68–4.70 (m, 1H, C*H*), 2.37 (s, 3H, Ar-CH_3), 1.55 (d, J = 6.8 Hz 3H, CHCH_3). ^{13}C NMR: δ 199.8.3, 141.5, 136.5, 132.8, 129.5, 128.9, 128.8, 128.5, 127.8, 126.9, 47.9, 19.5. MS: calcd. $C_{16}H_{16}O$: *m/z* 224.12.; found 225.1 $[M+H]^+$.

1-(4-Methoxyphenyl)-2-phenyl-1-propanone (4j)

Yellow oil. ^{1}H NMR: δ 7.97 (d, J = 9.2 Hz, 2H, *CO*-Ar*H*), 7.30–7.31 (m, 4H, CH-Ar*H*), 7.21–7.22 (m, 1H, CH-Ar*H*), 6.88 (d, J = 8.8 Hz, 2H, *CO*-Ar*H*), 4.64–4.69 (m, 1H, C*H*), 3.84 (s, 3H, OCH_3), 1.54 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR: δ 198.9, 142.3, 135.1, 129.2, 128.9, 127.7, 126.8, 47.7, 29.7, 21.6, 19.5. MS: calcd .$C_{16}H_{16}O_2$: *m/z* 240.12.; found 241.1 $[M+H]^+$.

1-(4-Chlorophenyl)-2-cyclopropyl-1-propanone (4l)

Yellow oil. ^{1}H NMR: δ 7.87 (d, J = 8.4 Hz, 2H, Ar*H*), 7.45 (d, J = 8.4 Hz, 2H, Ar*H*), 2.74–2.78 (m, 1H, CH_3-*CH*), 1.27 (d, J = 6.8 Hz, 3H, CHCH_3), 1.05–1.07 (m, 1H, CH_2C*H*), 0.56–0.57 (m, 2H, CH_2), 0.49–0.51 (m, 2H, CH_2). ^{13}C NMR: δ 202.8, 139.3, 135.3, 129.7, 128.9, 45.1, 16.9, 14.6, 4.36, 3.41. MS: calcd. $C_{12}H_{13}ClO$: *m/z* 208.07.; found 209.1 $[M+H]^+$.

1-(4-Chlorophenyl)-2-methyl-1-butanone (4m)

Yellow oil. ^{1}H NMR: δ 7.91 (d, J = 8.4 Hz, 2H, Ar*H*), 7.46 (d, J = 8.4 Hz, 2H, Ar*H*), 3.34–3.39 (m, 1H, C*H*), 1.80–1.88 (m, 1H, CH_2), 1.48–1.55 (m, 1H, CH_2), 1,20–1.28 (m, 3H, CHCH_3), 0.89–0.95 (m, 3H, CH_2CH_3). ^{13}C NMR: δ 203.1, 139.2, 135.2, 129.6, 128.9, 42.2, 26.6, 16.6, 11.7. MS: calcd. $C_{11}H_{13}ClO$: *m/z* 196.67; found 197.6 $[M+H]^+$.

(4-Chlorophenyl)-cyclohexylmethanone (4n)

Yellow oil.^{1}H NMR: δ 7. 91 (d, J = 8.8 Hz, 2H, Ar-*H*), 7.45 (d, J = 6.8 Hz, 2H, Ar*H*), 3.21–3.22 (m, 1H, CO-C*H*), 1.85–1.90 (m, 4H, CH_2), 1.27 (m, 6H, CH_2), ^{13}C NMR: δ 202.6, 139.1, 134.7, 129.7, 128.9, 45.7, 29.4, 26.9, 25.8. MS: calcd. $C_{13}H_{15}ClO$: *m/z* 222.08; found 223.2. $[M+H]^+$.

(4-Chlorophenyl)-cycloheptylmethanone (4o)

Yellow oil. ^{1}H NMR: δ 7.89 (d, J = 8.4 Hz, 2H, Ar*H*), 7.45 (d, J = 8.8 Hz, 2H, Ar*H*), 3.38–3.40 (m, 1H, CO-C*H*), 1.83–1.96 (m, 2H, CH_2), 1.80–1.82(m, 2H, CH_2), 1,70–1.76 (m, 6H, CH_2), 1.62–1.68 (m, 2H, CH_2). ^{13}C NMR: δ 202.9, 139.0, 134. 8, 129.7, 128.9, 46.7, 30.8, 28.3, 26.7. MS: calcd. $C_{14}H_{17}ClO$: *m/z* 236.10; found: $[M+H]^+$, 237.7 $[M+H]^+$.

Acknowledgments

The authors thank Professor Li-June Ming of the University of South Florida for carefully reading of the manuscript and constructive comments. We are grateful for financial support from the Natural Science Foundation of Shanghai. (NO. 17ZR14120 00).

Supplementary material

Experimental procedures and full characterization data for all compounds are available on the Journal's website.

Funding

The Natural Science Foundation of Shanghai (NO. 17ZR14120 00).

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