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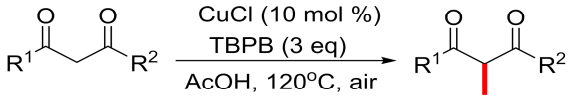

27 examples up to 90% yield

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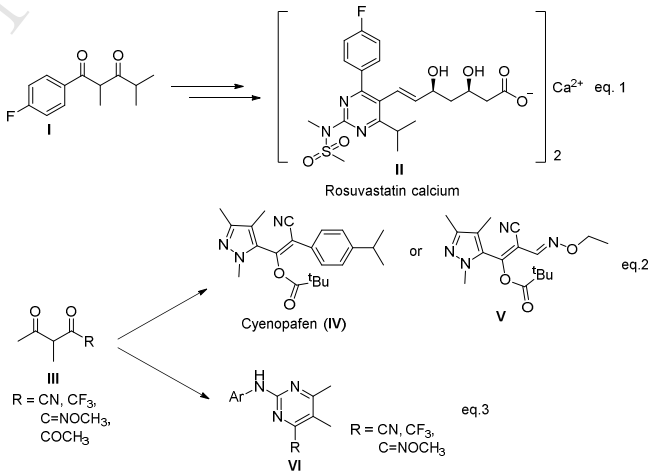
ABSTRACT

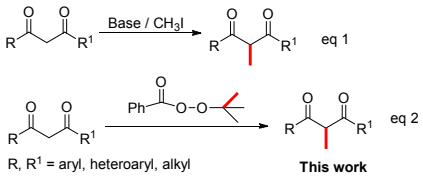
Copper-catalyzed radical methylation of 1,3-diketones with *tert*-butyl peroxybenzoate in air is described, providing a general pathway to α-methyl 1,3-diketones in moderate to good yields. This protocol has been scaled up to 50g, and one of the synthesized products can be used in the synthesis of medicine, Rosuvastatin.

1. Introduction

The introduction of methyl groups into organic molecules can improve the physical properties and bioactivities of biologically active molecules, hence, methylation reaction has aroused much interest in recent years. [1] α-Methyl-1,3-diketones are widely employed for the preparation of medicines and agrochemicals,[2] e.g. 1-(4-fluorophenyl)-2,4-dimethylpentane-1,3-dione (I) has been used for the preparation of Rosuvastatin calcium (II) (Scheme 1, eq 1) which could treat hyperchol-esterolemia, hyperlipoproteinemia and atherosclerosis; [3] α-Methyl-1,3-diketones (III) have been employed in the synthesis of pesticides (IV, V)[4] and fungicides (VI)[5] (Scheme 1, eqs 2 and 3). One of the most important routes to α-methyl-1,3-diketones is through methylation reaction. The traditional process involves the use of a strong base and poisonous methyl iodide (Scheme 2, eq 1). [3b, 6] Thus, the development of new routes and reagents for the methylation of 1,3-diketones is highly desirable. In 2008, the Li's group first reported that organic peroxides could be used as a methyl source for the methylation of arenes in the presence of palladium catalysts.[7] Thereafter, several groups have employed organic peroxides as the methylating reagent for N-, O- or C-methylation and oxidative methylation–cyclization of alkenes.[1c, 1f, 1g, 1h, 1k, 1l] In continuation of our effort on the organic peroxides promoted methylation of organic molecules,[8] herein, we report a novel methylation protocol for the preparation of α-methyl-1,3-diketones (Scheme 2, eq 2), this protocol features selective monomethylation in air with *tert*-butyl peroxybenzoate (TBPB), short reaction time (0.5 h), thus avoiding the use of poisonous methyl iodide, scaling up to 50g level, and applying the synthesized 1-(4-fluorophenyl)-2,4-dimethylpentane-1,3-dione (**I**) for synthesis of the medicine, Rosuvastatin.



Scheme 1. Application of α-methyl-1,3-diketones in medicines, pesticides and fungicides synthesis.



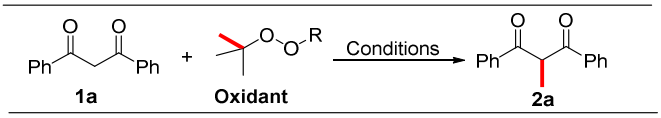
Scheme 2. α-Methylation of 1,3-diketones

2. Results and Discussion

Initially, we began by investigating the reaction of 1,3-diphenylpropane-1,3-dione (**1a**) with di-*tert*-butyl peroxide (DTBP) (1.0 mmol)) using CuI catalyst (10 mol %) in 10 mL AcOH under air at 100 °C. To our delight, the desired product **2a**

was obtained in a low yield of 33% (Table 1, entry 1). By increasing the amount of DTBP used, we found that an optimal use of 3 eq. of the oxidant resulted in an improved 71% yield of **2a** (Table 1, entries 2-4). No reaction was observed in the absence of CuI (Table 1, entry 5) which indicates that the Cu salt was essential for the formation of product. Also, we employed other Cu salts and found CuCl to be the most effective catalyst giving product **2a** in 87% yield (Table 1, entries 6-7). The choice of oxidant was also varied; when *tert*-butyl hydroperoxide (TBHP) was used in place of DTBP, the reaction became complex and only 30% yield of product **2a** could be obtained (Table 1, entry 8). However, the use of *tert*-butyl peroxybenzoate (TBPB) gave a very satisfactory yield of 91% (Table 1, entry 9). After screening the reaction temperature and time, the optimized reaction conditions were a combination of 1,3-diketone /TBPB/CuCl (1:3:0.1) in AcOH for 0.5 h under air at 120 °C (Table 1, entry 10).

Table 1. Optimization of the reaction conditions[a]

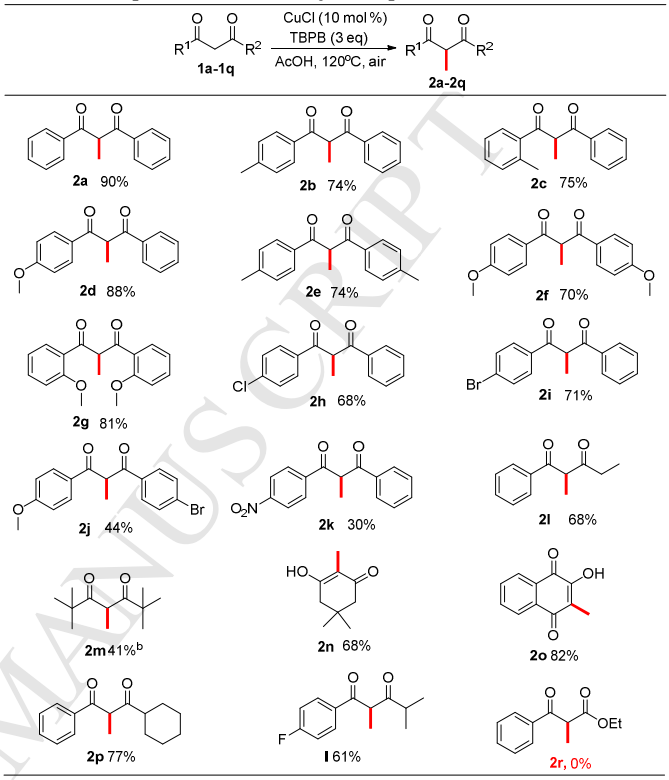


Entry	Catalyst	1a:Oxidant	Temp (°C)	Time (h)	Yield (%)[b]
1	CuI	1:1 (DTBP)	100	6	33
2	CuI	1:3 (DTBP)	100	6	71
3	CuI	1:6 (DTBP)	100	6	63
4	CuI	1:12 (DTBP)	100	6	60
5	None	1:3 (DTBP)	100	6	N.R.[c]
6	CuBr	1:3 (DTBP)	100	6	74
7	CuCl	1:3 (DTBP)	100	6	87
8	CuCl	1:3 (TBHP)	100	24	30
9	CuCl	1:3 (TBPB)	100	1.5	91
10	CuCl	1:3 (TBPB)	120	0.5	90
11	CuCl	1:3 (TBPB)	80	12	72
12	CuCl	1:3 (TBPB)	60	24	18
13	CuCl	1:3 (TBPB)	25	48	trace
14	$CuCl_2$	1:3 (TBPB)	120	0.5	53
15	$Cu(OTf)_2$	1:3 (TBPB)	120	0.5	50

[a] Reaction conditions: the mixture of **1a** (1.0 mmol), catalyst (10 mol %), and oxidant (di-*tert*-butyl peroxide (DTBP), *tert*-butyl hydroperoxide (TBHP), *tert*-butyl peroxybenzoate (TBPB)) was heated in HOAc (10 mL) under air.
[b] Isolated yield.
[c] N. R. means no reaction.

With the optimal reaction conditions in hand, we explored the scope of 1,3-dicarbonyl derivatives (**Table 2**). A variety of substituted aromatic, aliphatic and cyclic 1,3-diketones reacted with TBPB to give methylated products in moderate to good yields (30~90%). Electronic effect was found to play a significant role during the methylation process. With diketones bearing electron-donating groups on the aromatic rings, the reaction took place smoothly resulting in good yields (**2b-2g**). It is noteworthy that halogens were also tolerated under our copper-catalyzed protocol (**2h-2j, 2q**). However, low yields of products were obtained when the phenyl rings contains an electron-withdrawing substituent (e.g. **2k**) or different substituent types (e.g. **2j**). In addition, the reactions of unsymmetrical diketones containing aromatic-ethyl, aromatic-cyclohexyl and aromatic-isopropyl 1,3-dicarbonyl derivatives all occurred smoothly to afford methylated products, **2l**, **2p** and **I** in 68%, 77% and 61% yield respectively. Also, an enol substrate underwent methylation to produce a good yield of product **2o**. Remarkably, the reaction involving aliphatic and cyclic 1,3-diketones also occurred giving products **2m** and **2n** respectively; the low yield of **2m** (41%) may be attributed to the steric hindrance caused by the tertiary butyl group. Finally, the benzoyl ethyl acetate was reacted with TBPB, no reaction was observed (**2r**), hence this protocol is selective.

Table 2. Scope of 1,3-dicarbonyl compounds[a]



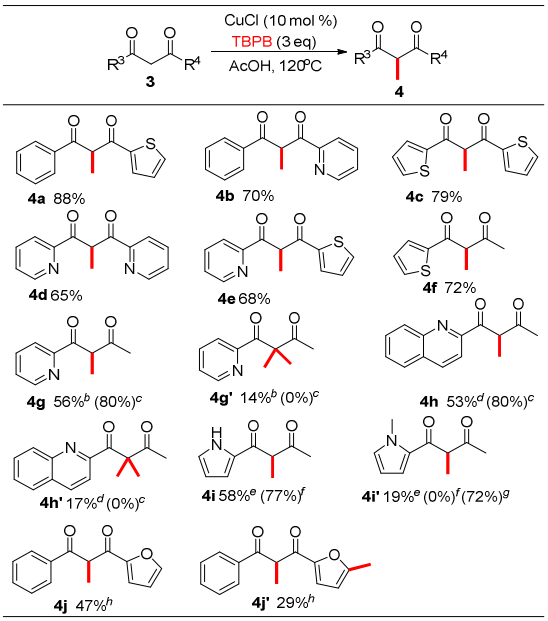
[a] Reaction conditions: the mixture of **1** (1.0 mmol), CuCl (10 mol %), and *tert*-butyl peroxybenzoate (TBPB) was heated in HOAc (10 mL) at 120 °C for 30 mins under air.

[b] The reaction was performed at 140 °C for 4h.

Subsequently, we investigated the scope of mono- or bis-heteroaryl 1,3-diketones. As shown in **Table 3**, a wide range of substrates reacted readily including both electron-deficient and electron-rich heteroaryls, thereby producing the corresponding methylated products in varying yields. Notably, *α*-monomethylation **4g** and bismethylation **4g'** were generated by substrate 1-(pyridin-2-yl)butane-1,3-dione **(3g)** under standard procedure, however only **4g** was produced when 1.2 equivalent TBPB was used. In addition, we found that the isolated product **4g** can be totally converted to **4g'** when reacted with 5 equivalents of TBPB; this result indicated that the bismethylation product was generated from the *α*-monomethylation compound. A reasonable explanation for this experimental result could be the chelation of the Cu salt with N-atom and methine carbon. [9] This metal-chelate function may activate the methine so that the bismethylation derivatives can also be generated. To verify this hypothesis, we carried out the reactions of substrates 1-(quinolin-2-yl)butane-1,3-dione **(3h)**, 1-(1*H*-pyrrol-2-yl)butane-1,3-dione (**3i**) and 1-(1-methyl-1*H*-pyrrol-2-yl)butane-1,3-dione (**3i'**) under standard conditions. Fortunately, a similar result was observed with **3h** where the ratio of derivatives **4h**/**4h'** was 3:1; with **3i** however, the bismethylation product was not detected but rather the N-methylation compound **4i'** after 10 minutes (see **footnote e**). Meanwhile, only product **4i'** was obtained when **3i'** was employed (see **footnote g**), this is probably because the angle of chelation between Cu salt and N-atom was too wide. Another

interesting result was the simultaneous formation of products **4j** and **4j'** even when TBPB was decreased to 0.99 equivalent. Thus, a competing reaction was taking place between *α*-monomethylation on 1,3-dicarbonyls and methylation on 2-furyl ring.

Table 3. Scope of 1,3-diketones bearing heteroaryl ring



[a] Reaction conditions: **3** (1.0 mmol), TBPB (3.0 mmol), CuCl (10 mol %) in HOAc (10 mL) at 120 □ for 30 mins under air except for otherwise noted;

[b] Generated by substrate **3g**, **4g**:**4g'** = 4:1;

[c] 1.2 mmol TBPB;

[d] Generated by substrate **3h**, **4h**:**4h'** = 3:1.

[e] Generated by substrate **3i**, **4i**:**4i'** =3:1;

[f] 10 mins;

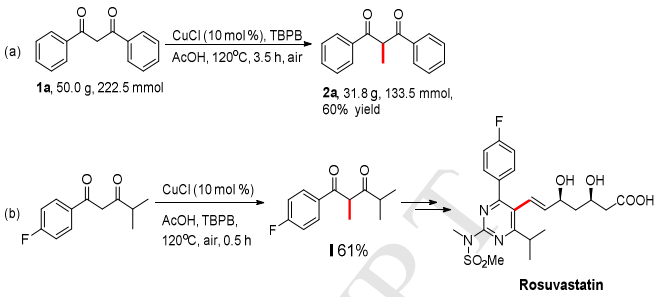
[g] Generated by substrate **3i'**;

[h] Generated by substrate **3j**, **4j**:**4j'** =1.6:1.

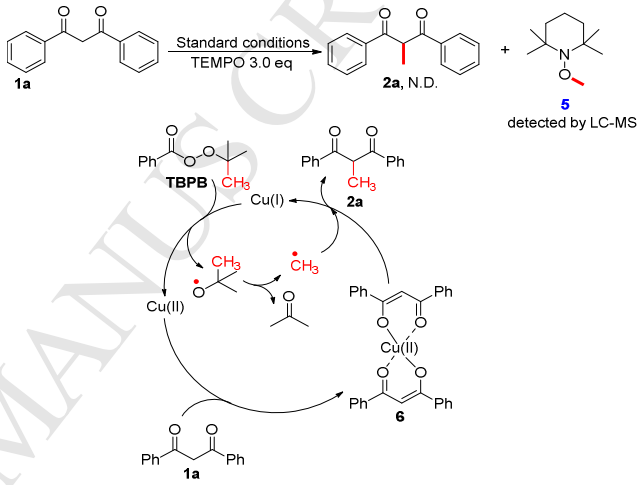
To further demonstrate the practicability of this methodology, 30 gram-scale preparation of *α*-mono-methylated 1,3-dicarbonyl compounds was performed as illustrated in Scheme 3 (a). 1,3-Diphenylpropane-1,3-dione **1a** (50.0 g, 222.5 mmol) was converted to **2a** (31.8 g, 133.5 mmol) in 60% isolated yield. Besides, another utility is shown in Scheme 3 (b), where I can be employed as an important intermediate in the synthesis of Rosuvastatin. Compared with the traditional method of synthesizing **I** which involves the use of poisonous MeI and refluxing for 48 h, this copper-catalyst protocol offers a friendly and rapid method of carrying out the *α*-monomethylation of 1-(4-fluorophenyl)-2,4-dimethylpent-ane-1,3-dione.

Furthermore, a radical capture experiment was conducted to help gain insight on the reaction pathway. As shown in Scheme 4, the addition of the widely known radical-scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 3.0 eq) inhibited the methylation reaction completely and **2a** was not detected. Moreover, the structure **5** formed from a methyl radical capture by TEMPO was detected by LC-MS, thus this result impliedstrongly the involvement of a radical intermediate.

On the basis of these experimental results, a proposed mechanism is outlined in Scheme 4. Initially, a *tert*-butoxy radical could be generated by single-electron transfer of Cu^{I} to TBPB, then it converted to a methyl radical through the loss of an acetone molecule. The Cu^{II} species generated from Cu^{I} by SET process, could coordinate with **1a** to form complex **6**, which was attacked by methyl radical to afford *α*-monomethylation product **2a** along with the release of Cu^{I}, which participated in the reaction again.



Scheme 3. Synthetic applications



Scheme 4. Radical capture experiment and proposed mechanism

3. Conclusion

In summary, we have developed a copper-catalyzed, direct and selective radical methylation of 1,3-diketones with *tert*-butyl peroxybenzoate, providing a friendly and general way for synthesis of *α*-methyl-1,3-diketones in moderate to good yields. This methodology involves neither the use of methyl iodide, or inert conditions. It requires a short reaction time and can be scaled up to 50g level. Also, the synthesized 1-(4-fluorophenyl)-2,4-dimethylpentane-1,3-dione was shown to be a vital starting material in the synthesis of the medicine, Rosuvastatin.

4. Experimental Section

4.1. General

^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were determined with $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts were reported in ppm from internal TMS (δ); all coupling constants (J values) were reported in hertz (Hz). High-resolution mass spectra were recorded on a TOF machine (ESI). Column chromatography was performed with 300−400 mesh silica gel using flash column techniques. All of the reagents were obtained commercially and used directly unless otherwise noted.

4.2. General procedure for the methylation of 1,3-diketones (1 and 3).

*Typical procedure for the preparation of 2-methyl-1,3-diphenylpropane-1,3-dione (**2a**).* To a solution of acetic acid (10 mL) containing 1,3-diphenylpropane-1,3-dione (**1a**) (0.224 g, 1.0 mmol) and CuCl (0.010 g, 0.1 mmol) was added *tert*-butyl peroxybenzoate (0.56 mL, 3.0 mmol), then the mixture was heated at 120 □ for 0.5 hours, after completion of reaction (monitored by TLC), the solvent was removed under vacuum and the residue was neutralized by aqueous $NaHCO_3$ solution and extracted with DCM (10 mL × 3). The combined organic fractions were dried over anhydrous $MgSO_4$, and concentrated under vacuum to obtain the crude product, which was purified by column chromatography (silica gel, petroleum ether/EtOAc (95:5)) to give pure 2-methyl-1,3-diphenylpropane-1,3-dione (**2a**).

*Scale-up procedure for the preparation of 2-methyl-1,3-diphenylpropane-1,3-dione (**2a**).* To a three-necked flask were added acetic acid (450 mL), 1,3-diphenylpropane-1,3-dione (**1a**) (50.0 g, 222.5 mmol) and CuCl (2.207 g, 22.3 mmol). After the mixture was heated to 120 ℃, *tert*-butyl peroxybenzoate (124.5 mL, 669 mmol) was added in dropwise for 1 hour, then stirred for about 2.5 hours. After completion of reaction (monitored by TLC), the solvent was removed under vacuum and dichloromethane (200 mL) was added to the residue, filtered with celite. The filtrate was washed with water (300 mL × 3), neutralized by aqueous $NaHCO_3$ solution, and concentrated under vacuum to obtain the red oily crude product, which was recrystallized from petroleum ether to give pure 2-methyl-1,3-diphenylpropane-1,3-dione (**2a**, 31.8 g, 60% yield).

4.3 Characterization

*2-Methyl-1,3-diphenylpropane-1,3-dione (**2a**)* [9]

Colorless solid, 90% yield (214 mg), mp 75−79 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99−7.92 (m, 4H), 7.60−7.53 (m, 2H), 7.50−7.41 (m, 4H), 5.27 (q, *J* = 7.0 Hz, 1H), 1.61 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.3, 135.8, 133.6, 129.0, 128.7, 51.2, 14.5. MS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{16}H_{15}O_2$ 239.1, found 239.1.

*2-Methyl-1-phenyl-3-(p-tolyl)propane-1,3-dione (**2b**)* [9]

Colorless solid, 74% yield (186 mg), mp 92–95 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98–7.92 (m, 2H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.58–7.52 (m, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 5.24 (q, *J* = 7.0 Hz, 1H), 2.40 (s, 3H), 1.59 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.4, 197.0, 144.6, 135.8, 133.5, 133.2, 129.7, 129.0, 128.8, 128.6, 51.1, 21.8, 14.5. MS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{17}H_{17}O_2$ 253.1, found 253.1.

*1-Phenyl-3-(o-tolyl)propane-1,3-dione (**2c**)*[10]

There is an equilibrium of keto/enol in $CDCl_3$ solution for **2c**, in which keto is major. Yellow oil, 75% yield (189 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97–7.90 (m, 1.98H, keto/enol), 7.70–7.63 (m, 1.41H, keto/enol), 7.61–7.53 (m, 1.05H, keto/enol), 7.52–7.42 (m, 2.65H, keto/enol), 7.41–7.32 (m, 1.26H, keto/enol), 7.31–7.20 (m, 2.85H, keto/enol), 5.22 (q, *J* = 7.0 Hz, 1H, keto), 2.45 (s, 3H, keto), 2.37 (s, 0.56H, enol), 1.75 (s, 0.53H, enol), 1.60 (d, *J* = 7.0 Hz, 3H, keto). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.6 (keto), 197.5 (keto), 192.2 (enol), 189.4 (enol), 139.4, 137.5, 137.3, 137.0, 136.1, 134.7, 133.5, 132.4, 131.7, 130.7, 130.6, 129.4, 128.9, 128.6, 128.3, 128.1, 126.7, 125.83, 125.77, 105.4, 53.2 (keto), 21.3 (keto), 19.3 (enol), 15.5 (enol), 14.4 (keto). MS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{17}H_{17}O_2$ 253.1, found 253.1.

*1-(4-Methoxyphenyl)-2-methyl-3-phenylpropane-1,3-dione (**2d**)* [9]

Yellow oil, 88% yield (236 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.90 (m, 4H), 7.58–7.51 (m, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 6.98–6.89 (m, 2H), 5.22 (q, *J* = 7.0 Hz, 1H), 3.85 (s, 3H), 1.58 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.4, 196.0, 163.9, 135.8, 133.5, 131.0, 128.9, 128.6, 114.2, 55.6, 51.0, 14.6. MS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{17}H_{17}O_3$ 269.1, found 269.1.

*2-Methyl-1,3-bis (p-tolyl) propane-1,3-dione (**2e**)* [11]

Yellow solid, 74% yield (197 mg), mp 135–137 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.3 Hz, 4H), 7.23 (d, *J* = 8.0 Hz, 4H), 5.20 (q, *J* = 7.0 Hz, 1H), 2.39 (s, 6H), 1.58 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.1, 144.5, 133.3, 129.7, 128.8, 51.2, 21.8, 14.6. MS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{18}H_{19}O_2$ 267.1, found 267.1.

*1,3-Bis(4-methoxyphenyl)-2-methylpropane-1,3-dione (**2f**)* [12]

Yellow oil, 70% yield (209 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.9 Hz, 4H), 6.89 (d, *J* = 8.9 Hz, 4H), 5.18 (q, *J* = 7.0 Hz, 1H), 3.80 (s, 6H), 1.55 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.0, 163.7, 130.8, 128.6, 114.0, 55.4, 50.6, 14.5. MS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{18}H_{19}O_4$ 299.1, found 299.1.

*1,3-Bis(2-methoxyphenyl)-2-methylpropane-1,3-dione (**2g**)*

Colorless solid, 81% yield (241 mg), mp 134–136 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.40–7.47 (m, 2H), 6.99 (t, *J* = 7.5 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 5.45 (q, *J* = 7.0 Hz, 1H), 3.68 (s, 6H), 1.45 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.6, 158.5, 133.9, 131.4, 126.9, 120.9, 111.5, 59.3, 55.2, 13.3. HRMS (CI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{18}H_{19}O_4$ 299.1283, found 299.1294.

*1-(4-Chlorophenyl)-2-methyl-3-phenylpropane-1,3-dione (**2h**)* [13]

Yellow oil, 68% yield (185 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.93 (m, 2H), 7.91–7.84 (m, 2H), 7.62–7.54 (m, 1H), 7.51–7.37 (m, 4H), 5.20 (q, *J* = 7.0 Hz, 1H), 1.60 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.2, 196.0, 140.1, 135.6, 134.2, 133.8, 130.0, 129.4, 129.1, 128.7, 51.3, 14.5. MS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{16}H_{14}ClO_2$ 273.1, found 273.1.

*1-(4-Bromophenyl)-2-methyl-3-phenylpropane-1,3-dione (**2i**)*

Yellow oil, 71% yield (224 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.92 (m, 2H), 7.91–7.85 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.52–7.38 (m, 4H), 5.20 (q, *J* = 7.0 Hz, 1H), 1.60 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.2, 196.1, 140.1, 135.6, 134.1, 133.8, 129.5, 129.4, 129.1, 128.7, 51.3, 14.5. HRMS (CI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{16}H_{14}BrO_2$ 317.0177, found 317.0189.

*1-(4-Bromophenyl)-3-(4-methoxyphenyl)-2-methylpropane-1,3-dione (**2j**)*

Colorless solid, 44% yield (152 mg), mp 96–98 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 9.0 Hz, 2H), 7.79 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 5.12 (q, *J* = 7.0 Hz, 1H), 3.87 (s, 3H), 1.59 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.4, 195.8, 164.1, 134.7, 132.3, 131.1, 130.1, 128.7, 128.5, 114.3, 55.7, 51.4, 14.6. HRMS (CI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{17}H_{16}BrO_3$ 347.0283, found 347.0296.

*2-Methyl-1-(4-nitrophenyl)-3-phenylpropane-1,3-dione (**2k**)*

Yellow oil, 30% yield (85 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (d, *J* = 8.9 Hz, 2H), 8.18 (d, *J* = 8.9 Hz, 2H), 8.05–7.99 (m, 2H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H),

5.91 (q, *J* = 6.9 Hz, 1H), 1.41 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 198.1, 197.2, 150.1, 140.3, 135.0, 134.0, 129.6, 129.1, 128.6, 124.2, 50.3, 13.9. HRMS (CI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{16}H_{14}NO_4$ 284.0923, found 284.0934.

*2-Methyl-1-phenylpentane-1,3-dione (**2l**)* [14]

Yellow oil, 68% yield (129 mg); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.00−7.92 (m, 2H), 7.61–7.53 (m, 1H), 7.51–7.42 (m, 2H), 4.50 (q, *J* = 7.0 Hz, 1H), 2.61–2.48 (m, 1H), 2.47–2.32 (m, 1H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 207.8, 197.6, 136.1, 133.7, 129.0, 128.7, 56.0, 34.1, 13.8, 7.8. MS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{15}O_2$ 191.1, found 191.1.

*2,2,4,6,6-Pentamethylheptane-3,5-dione (**2m**)* [15]

Colorless oil, 41% yield (81 mg); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 4.45 (q, *J* = 6.9 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.15 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 212.1, 49.0, 44.6, 27.5, 15.7. MS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{23}O_2$ 199.2, found 199.2.

*3-Hydroxy-2,5,5-trimethylcyclohex-2-en-1-one (**2n**)* [16]

Yellow oil, 68% yield (105 mg); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.37 (s, 1H), 3.70 (s, 3H), 2.28 (s, 2H), 2.22 (s, 2H), 1.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 199.7, 177.1, 101.3, 55.8, 50.9, 42.8, 32.7, 28.4. MS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_9H_{15}O_2$ 155.1, found 155.1.

*2-Hydroxy-3-methylnaphthalene-1,4-dione (**2o**)*

Yellow solid, 82% yield (154 mg), mp 164–166 □. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.13 (dd, *J* = 7.6, 1.0 Hz, 1H), 8.08 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.75 (td, *J* = 7.6, 1.4 Hz, 1H), 7.68 (td, *J* = 7.5, 1.3 Hz, 1H), 7.31 (s, 1H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 185.2, 181.3, 153.3, 135.0, 133.0, 129.6, 126.9, 126.3, 120.7, 8.8. HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ Calcd for $C_{11}H_8NaO_3$ 211.0371, found 211.0365.

*1-Cyclohexyl-2-methyl-3-phenylpropane-1,3-dione (**2p**)*

Yellow oil, 82% yield (188 mg). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.00–7.92 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 4.60 (q, *J* = 7.0 Hz, 1H), 2.56–2.44 (m, 1H), 1.85–1.65 (m, 4H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.31–1.10 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 210.3, 197.8, 136.3, 133.7, 129.0, 128.7, 54.8, 49.6, 29.4, 28.8, 25.8, 25.5, 13.8. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{16}H_{21}O_2$ 245.1541, found 245.1542.

*1-(4-Fluorophenyl)-2,4-dimethylpentane-1,3-dione (**I**)*

Colorless oil, 61% yield (135 mg). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.05–7.89 (m, 2H), 7.19–7.09 (m, 2H), 4.57 (q, *J* = 7.0 Hz, 1H), 2.80–2.69 (m, 1H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 210.9, 196.0, 166.1 (d, *J* = 256.5 Hz), 132.6 (d, *J* = 3.0 Hz), 131.5 (d, *J* = 10.0 Hz), 116.1 (d, *J* = 20.0 Hz), 54.7, 39.4, 19.2, 18.7, 13.8. HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ Calcd for $C_{13}H_{15}FNaO_2$ 245.0954, found 245.0955.

*2-Methyl-1-phenyl-3-(thiophen-2-yl)propane-1,3-dione (**4a**)*

Yellow oil, 88% yield (214 mg). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.02–7.95 (m, 2H), 7.73 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.65 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.60–7.52 (m, 1H), 7.50–7.40 (m, 2H), 7.14–7.08 (m, 1H), 5.08 (q, *J* = 7.0 Hz, 1H), 1.63 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 196.6, 189.0, 143.1, 135.9, 134.6, 133.7, 132.8, 129.0, 128.8, 128.5, 53.1, 14.8. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{14}H_{13}O_2S$ 245.0636, found 245.0624.

*2-Methyl-1-phenyl-3-(pyridin-2-yl)propane-1,3-dione (**4b**)*

Yellow oil, 70% yield (167 mg). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.52 (d, *J* = 4.3 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 8.07–8.03 (m, 2H), 7.83 (td, *J* = 7.7, 1.6 Hz, 1H), 7.61–7.52 (m, 1H), 7.51–7.45 (m, 2H), 7.44–7.38 (m, 1H), 5.74 (q, *J* = 7.0 Hz, 1H), 1.52 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 198.8, 198.7, 151.9, 148.9, 137.2, 136.4, 133.1, 128.9, 128.8, 127.4, 122.6, 49.7, 13.5. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{14}NO_2$ 240.1024, found 240.1025.

*2-Methyl-1,3-di(thiophen-2-yl)propane-1,3-dione (**4c**)*

Yellow oil, 79% yield (197 mg). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.78 (dd, *J* = 3.9, 1.0 Hz, 2H), 7.66 (dd, *J* = 5.0, 1.0 Hz, 2H), 7.14–7.08 (m, 2H), 4.90 (q, *J* = 7.0 Hz, 1H), 1.64 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 189.3, 143.0, 134.8, 133.0, 128.6, 54.9, 14.9. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{12}H_{11}O_2S_2$ 251.0200, found 251.0195.

*2-Methyl-1,3-di(pyridin-2-yl)propane-1,3-dione (**4d**)*

Yellow oil, 65% yield (156 mg). ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 8.54 (d, *J* = 4.3 Hz, 2H), 8.00 (d, *J* = 3.9 Hz, 4H), 7.63–7.54 (m, 2H), 5.77–5.67 (m, 1H), 1.39 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): *δ* 198.6, 151.3, 148.9, 137.8, 127.6, 121.9, 49.2, 12.9. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{14}H_{13}N_2O_2$ 241.0977, found 241.0971.

*2-Methyl-1-(pyridin-2-yl)-3-(thiophen-2-yl)propane-1,3-dione (**4e**)*

Yellow solid, 68% yield (167 mg), mp 82–83 □. ^{1}H NMR (400 MHz, $CDCl_3$) : *δ* 8.56 (d, *J* = 4.3 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.85–7.80 (m, 2H), 7.64 (d, *J* = 4.9 Hz, 1H), 7.48–7.40 (m, 1H), 7.16–7.10 (m, 1H), 5.65 (q, *J* = 7.1 Hz, 1H), 1.56 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 1987.9, 191.1, 151.8, 148.9, 143.6, 137.3, 134.0, 132.7, 128.3, 127.5, 122.7, 51.0, 13.9. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{13}H_{12}NO_2S$ 246.0589, found 246.0588.

*2-Methyl-1-(thiophen-2-yl)butane-1,3-dione (**4f**)*

Yellow oil, 72% yield (131 mg). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.79 (d, *J* = 3.8 Hz, 1H), 7.72 (d, *J* = 4.9 Hz, 1H), 7.17 (t, *J* = 4.4 Hz, 1H), 4.33 (q, *J* = 7.0 Hz, 1H), 2.19 (s, 3H), 1.48 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 204.4, 189.8, 143.3, 135.1, 133.3, 128.6, 58.2, 27.8, 13.7. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_9H_{11}O_2S$ 183.0480, found 183.0478.

*2-Methyl-1-(pyridin-2-yl)butane-1,3-dione (**4g**)*

Yellow oil, 56% yield (99 mg). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.65 (d, *J* = 4.2 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.85 (td, *J* = 7.7, 1.6 Hz, 1H), 7.51–7.44 (m, 1H), 4.89 (q, *J* = 7.1 Hz, 1H), 2.36 (s, 3H), 1.41 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 206.3, 198.4, 152.1, 148.9, 137.2, 127.5, 122.5, 54.8, 29.5, 12.6. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{10}H_{12}NO_2$ 178.0868, found 178.0867.

*2,2-Dimethyl-1-(pyridin-2-yl)butane-1,3-dione (**4g'**)*

Yellow oil, 14% yield (26 mg). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.59 (d, *J* = 4.2 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.84 (td, *J* = 7.7, 1.6 Hz, 1H), 7.46–7.38 (m, 1H), 2.21 (s, 3H), 1.45 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 207.8, 200.9, 151.2, 148.3, 137.3, 127.1, 123.5, 29.7, 26.8, 22.8. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{11}H_{14}NO_2$ 192.1025, found 192.1021.

*2-Methyl-1-(quinolin-2-yl)butane-1,3-dione (**4h**)*

Yellow oil, 53% yield (118 mg). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.28 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.82–7.74 (m, 1H), 7.69–7.60 (m, 1H), 5.09 (q, *J* =

7.1 Hz, 1H), 2.49 (s, 3H), 1.47 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 206.4, 198.5, 151.6, 147.1, 137.4, 130.4, 130.3 129.9, 128.9, 127.9, 118.6, 54.9, 29.8, 12.7. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{14}H_{14}NO_2$ 228.1025, found 228.1017.

*2,2-Dimethyl-1-(quinolin-2-yl)butane-1,3-dione (**4h'**)*

Colorless solid, 17% yield (41 mg), mp 62–63 □. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.29 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.81–7.73 (m, 1H), 7.69–7.60 (m, 1H), 2.32 (s, 3H), 1.53 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 207.7, 201.2, 150.5, 146.6, 137.4, 130.32, 130.30, 129.6, 129.0, 127.8, 119.3, 59.1, 27.0, 23.1. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{16}NO_2$ 242.1181, found 242.1180.

*2-Methyl-1-(1H-pyrrol-2-yl)butane-1,3-dione (**4i**)*

Yellow oil, 58% yield (96 mg). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 10.01 (s, 1H), 7.12 (s, 1H), 7.01 (s, 1H), 6.34–6.28 (m, 1H), 4.22 (q, *J* = 7.0 Hz, 1H), 2.17 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 204.9, 187.0, 131.2, 126.4, 118.1, 111.3, 56.9, 28.1, 13.8. HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ Calcd for $C_9H_{11}NNaO_2$ 188.0687, found 188.0687.

*2-Methyl-1-(1-methyl-1H-pyrrol-2-yl)butane-1,3-dione (**4i'**)*

Yellow oil, 72% yield (129 mg). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.03 (dd, *J* = 4.2, 1.6 Hz, 1H), 6.90–6.85 (m, 1H), 6.19–6.14 (m, 1H), 4.23 (q, *J* = 7.0 Hz, 1H), 3.95 (s, 3H), 2.16 (s, 3H), 1.40 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 205.4, 187.4, 132.4, 130.2, 120.7, 108.7, 57.6, 37.9, 27.9, 14.0. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{10}H_{14}NO_2$ 180.1025, found 180.1016.

*Mixture of 1-(furan-2-yl)-2-methyl-3-phenylpropane-1,3-dione (**4j**)* and *2-methyl-1-(5-methylfuran-2-yl)-3-phenylpropane-1,3-dione (**4j'**)*

Yellow oil, **4j**/**4j'** = 1/0.6 (calculated on the basis of ^{1}H NMR integral), total yield 76% (178 mg). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.03–7.95 (m, 3.23H), 7.60–7.51 (m, 2.72H), 7.50–7.41 (m, 3.31H), 7.25 (dd, *J* = 3.6, 0.6 Hz, 0.93H), 7.16 (d, *J* = 3.5 Hz, 0.62H), 6.52 (dd, *J* = 3.6, 1.7 Hz, 0.98H), 6.15 (dd, *J* = 3.5, 0.8 Hz, 0.61H), 5.09 (q, *J* = 7.1 Hz, 1H), 5.01 (q, *J* = 7.0 Hz, 0.62H), 2.32 (s, 1.91H), 1.56 (d, *J* = 7.1 Hz, 5.01H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 197.1, 197.0, 186.1, 185.3, 158.3, 151.8, 150.3, 146.7, 136.2, 136.0, 133.6, 133.5, 128.94, 128.87, 128.71, 128.69, 120.3, 118.1, 112.8, 109.6, 51.8, 51.7, 14.2, 13.8. HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{14}H_{13}O_3$ 229.0865, found 229.0859; $(M+H)^+$ Calcd for $C_{15}H_{15}O_3$ 243.1021, found 243.1029.

*1-Methoxy-2,2,6,6-tetramethylpiperidine (**5**)*

MS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{10}H_{22}NO$ 172.2, found 172.2.

Supplementary data

Experimental procedures, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra for the products are available.

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