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DDQ-mediated oxidation of sp^3 C–H bond for the direct synthesis of vicinal tricarbonyl compounds

Zheng-Lin Wang, Xing-Lan An, Li-Shi Ge, Jing-Hai Jin, Xiaoyan Luo *, Wei-Ping Deng *

Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, PR China

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Dedicated to academician Li-Xin Dai on the occasion of his 90th birthday

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ABSTRACT

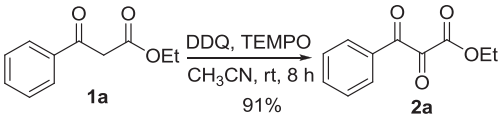
A facile and direct synthetic method was developed for the construction of vicinal tricarbonyl compounds (VTCs) in moderate to excellent yields (46–92%), by treating the readily available 1,3-dicarbonyl compounds with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The reaction pathway involves the DDQ-mediated oxidative activation of sp^3 C–H bond and subsequent coupling to TEMPO to form the key intermediate TEMPO-substrate adduct, which can be further converted to VTC products promoted by DDQ.

1. Introduction

Vicinal tricarbonyl compounds (VTCs) are not only the key structural units in biologically active natural products,[1] such as the potent immunosuppressant FK-506,[1a–c] Rapamycin,[1d] and 29-demethoxyrapamycin,[1e] and other biologically complicated compounds,[2] but also employed as useful building blocks in synthetic organic chemistry.[3] Vicinal tricarbonyl compounds, characterized by the highly electrophilic nature of carbonyl groups, particularly the central carbonyl, can be easily attacked by variety of nucleophilic substrates. Therefore, these compounds have been successfully applied to the preparation of various heterocyclic compounds,[4] biologically active antibiotics,[5] potent inhibitors of hydrolytic enzymes,[6] and other compounds.[7]

In view of the synthetic versatility of VTCs, many synthetic methods have been developed for the synthesis of VTCs.[3] Especially, Wasserman[3a,4a–j,8] and his co-workers have made important contributions in this field. Generally, most of these synthetic strategies rely on α-functionalization of 1,3-dicarbonyl compounds, which preinstalls a suitable functional group between two carbonyls, followed by oxidation with appropriate oxidants.[9] However, the synthesis of VTCs through a straightforward oxidation of sp^3 C–H bond of 1,3-dicarbonyl compounds has been rarely reported.[10] Recently, Kirsch and his co-workers demonstrated a direct pathway for the formation of VTCs via IBX-mediated oxygenations of β-keto esters in moderate yields, which shows great attraction for a straightforward synthesis of VTCs, although only two examples were reported.[11] Although, most of the synthetic methods have been developed through a pre-functionalization of 1,3-dicarbonyl compounds, a direct oxidative activation of sp^3 C–H bond and subsequent oxygenation is the most straightforward strategy for the formation of VTCs.

In the course of developing new methods for oxidative activation of sp^3 C–H bond and corresponding coupling,[12] we recently demonstrated a facile approach to afford 2,3-dicyanofurans and thiophenes from 1,3-dicarbonyl compounds via DDQ-mediated oxidative coupling.[13] To investigate the mechanism of this transformation, we performed a reaction of ethyl benzoylacetate **1a** with DDQ in the presence of TEMPO as radical trapping reagent. Unexpectedly, only trace amount of 2,3-dicyanofuran was observed[13] and vicinal tricarbonyl compound **2a** was obtained in 91% yield (Scheme 1). This interesting finding prompted us to further develop this new protocol for facile and direct construction of VTCs from



1a 2a

Scheme 1. The TEMPO trapping experiment of **1a** in the presence of DDQ.

* Corresponding authors. Tel./fax: +86 021 6425 2431; e-mail addresses: xyluo@ecust.edu.cn (X. Luo), weiping_deng@ecust.edu.cn (W.-P. Deng).

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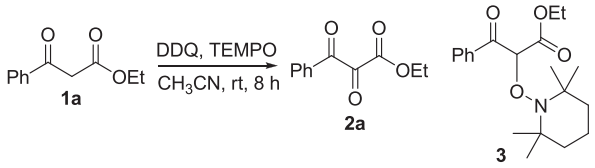
readily available starting materials under mild conditions. Herein, we would like to describe full details regarding the direct synthesis of vicinal tricarbonyl compounds from 1,3-dicarbonyl compounds by reacting with TEMPO using DDQ as an oxidant.

2. Results and discussion

With encouragement of the efficient formation of VTC **2a** (Scheme 1) and its potential utility as building block for the synthesis of important bioactive compounds, we then further optimized the reaction conditions (Table 1). Although, initial use of 3 equiv of DDQ and TEMPO gave **2a** in excellent yield (Table 1, entry 1), it was found that the reaction still proceeded smoothly by the decrease of amount of both DDQ and TEMPO to 1.0 equiv, providing the product **2a** in comparable yield (Entry 3), and the optimal result was obtained when using 1.1 equiv of DDQ and 1.2 equiv of TEMPO in CH_3CN under nitrogen atmosphere. It was further found that comparable yields were obtained under either air or nitrogen atmosphere (Entries 4 and 5). However, 0.5 equiv of DDQ and 1.2 equiv of TEMPO led to **2a** and **3** in 31% and 35% yields, respectively (Entry 7). 1.0 equiv of DDQ and 0.5 equiv of TEMPO resulted in the formation of **2a** in only 45% yield (Entry 8). Meanwhile, no any product **2a** was observed in the absence of either DDQ or TEMPO (Entries 9 and 10).

Table 1
Optimization of the reaction conditions[a]



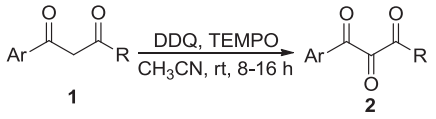
Entry	DDQ (equiv)	TEMPO (equiv)	Yield[b] (%)
1	3.0	3.0	91
2	2.0	2.0	90
3	1.0	1.0	85
4	1.1	1.2	92
5[c]	1.1	1.2	91
6	0.8	1.2	82
7[d]	0.5	1.2	31
8	1.0	0.5	45
9	0	1.0	0
10[e]	1.0	0	0

[a] Reaction condition: **1a** (0.2 mmol), DDQ, and TEMPO in 2 mL CH_3CN under N_2 at room temperature.
[b] Isolated yield of **2a**.
[c] Under air.
[d] Compound **3** was obtained in 35% yield.
[e] Only 2,3-dicyanofuran was observed.

In order to understand the generality and scope of this facile formation of VTCs, a number of 1,3-dicarbonyl compounds were investigated, as shown in Table 2. It was found that ethyl and methyl benzoylacetate both reacted smoothly with TEMPO in the presence of DDQ, affording the VTC products **2a**, **b** in excellent yields (Table 2, entries 1 and 2). Substrates bearing electron-withdrawing and -donating substituents on aryl ring, such as methyl, methoxyl, chloro, and bromo afforded the corresponding VTCs in good to excellent yields (Entries 3–7). Likewise, other aryl substrates containing naphthyl and thienyl groups also showed good reactivity to obtain VTCs **2h** and **2i** in moderate to excellent yields (Entries 8 and 9). In addition, β-diketones **1k** and **1l**, as well as β-ketoamides **1m** and **1n** could also be converted to corresponding VTCs **2k**–**n** in good to excellent yields (Entries 11–14).

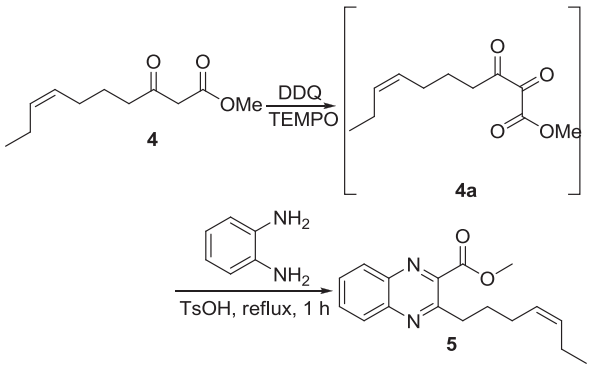
It is notable that an attempt to purify aliphatic VTC product **4a** by flash chromatography on silica gel was not successful. To prove the formation of **4a**, the reaction mixture of aliphatic 1,3-dicarbonyl compound **4** with DDQ and TEMPO was in situ treated with *o*-phenylenediamine, and just as we expected quinoxaline derivative **5** was obtained in 53% yield in one pot (Scheme 2).[14]

Table 2
Substrate scope for the direct synthesis of VTCs from 1,3-dicarbonyl compounds[a]



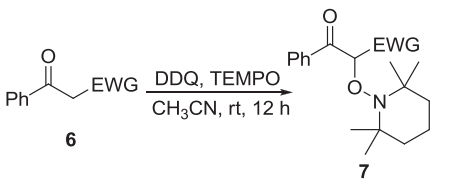
Entry	Ar	R	Products	Yield[b] (%)
1	C_6H_5	OEt	**2a**	91
2	C_6H_5	OMe	**2b**	90
3	4-MeC_6H_4	OMe	**2c**	90
4	4-$MeOC_6H_4$	OMe	**2d**	64
5	4-ClC_6H_4	OMe	**2e**	85
6	4-BrC_6H_4	OMe	**2f**	64
7	3-BrC_6H_4	OMe	**2g**	77
8	2-Naphthyl	OMe	**2h**	88
9	2-Thienyl	OMe	**2i**	87
10	5-Cl-2-thienyl	OMe	**2j**	46
11	C_6H_5	Me	**2k**	65[c]
12	C_6H_5	C_6H_5	**2l**	92[c]
13	C_6H_5	NMe_2	**2m**	55
14	C_6H_5	NHEt	**2n**	80

[a] Reaction condition: **1** (0.2 mmol), DDQ (0.22 mmol), TEMPO (0.24 mmol) in 2 mL CH_3CN at room temperature.
[b] Isolated yield.
[c] Determined by ^1H NMR.



Scheme 2. The synthesis of quinoxaline derivative **5** from **4**.

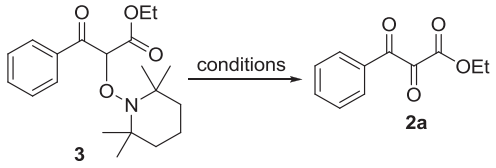
Next, we further extended the reaction scope to methylsulfonyl- and nitro-ketone compounds **6a** and **6b**. Interestingly, the stable TEMPO-substrate adducts **7a** and **7b** instead of the corresponding VTCs were obtained in moderate yields, respectively (Scheme 3), which implies that an α-carbonyl radical does form since it can be easily trapped by TEMPO to afford **7a** and **7b**.



Scheme 3. α-Oxyamination reactions between **6** and TEMPO.

Inspired by the formation of compounds **3**, **7a**, and **7b**, we speculated that these TEMPO-substrate adducts could be the key intermediates, which can be further transformed to VTC products **2** in the presence of DDQ. In order to prove our hypothesis, intermediate **3** was treated with DDQ and led to the formation of VTC product **2a** in excellent yield (Table 3, entry 1). As reported by Tan,[15] the adduct **3** was found quite stable and can only gradually decomposed to afford **2a** in 12% yield in the absence of DDQ at room temperature under air atmosphere (Table 3, entry 2). Additionally, our initial experiment (Table 1, entry 7) showed that the adduct **3** was obtained in 35% yield, when 0.5 equiv of DDQ was used. These observations indicate that DDQ could also promote the formation of VTC product **2** from TEMPO-substrate adducts.

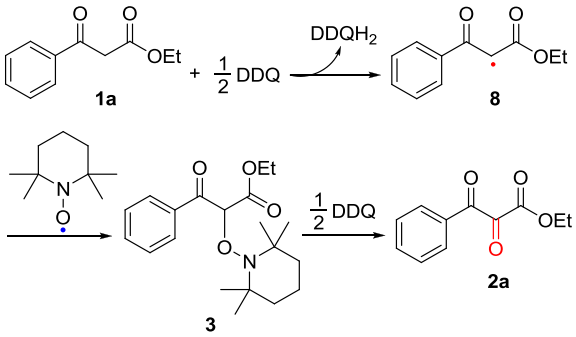
Table 3
Treatment of **3** and DDQ to **2a**[a]



Entry	DDQ (equiv)	Time (h)	Yield[b] (%)
1	1.1	42	90
2	0	480[c]	12

[a] Reaction condition: **3** (0.2 mmol), DDQ (0.22 mmol) in 2 mL CH_3CN at room temperature.
[b] Isolated yield.
[c] No additive was added.

Based on these findings and our previous results,[13] we proposed a reaction pathway for this transformation shown in Scheme 4. A single electron transfer (SET) from carbonyl compound **1a** to DDQ generates radical **8**, which then couples to TEMPO to form the intermediate TEMPO-substrate adduct **3**. According to this hypothesis, only 0.5 equiv of DDQ was needed in the first step, which is supported by the result of entry 7 in Table 1. Finally, another 0.5 equiv of DDQ is consumed to promote the formation of vicinal tricarbonyl compound **2a** from TEMPO-substrate adduct **3**.[16]



Scheme 4. Proposed reaction pathway.

3. Conclusion

In conclusion, we have demonstrated a facile method for the direct synthesis of vicinal tricarbonyl compounds from readily available 1,3-dicarbonyl compounds in moderate to excellent yields through DDQ-mediated oxidative activation of sp^3 C–H bond and subsequent coupling to TEMPO. To the best of our knowledge, it is the first time to find that the in situ formed key intermediate, TEMPO-substrate adduct, can be easily converted to VTC products promoted by the excess amount of DDQ. From a synthetic point of view, this protocol represents a facile and direct approach for the construction of VTCs in one pot process, which might be useful in biological scenarios. Further studies on the applications of this transformation are underway in our laboratory.

4. Experimental section

4.1. General

Column chromatography was carried out on 100–200 silica gel. All reagents and solvents were used as purchased unless otherwise noted. ^1H NMR spectra were recorded on 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$ using TMS as internal standard. Melting points were obtained in open capillary tubes using a micro melting point apparatus and were uncorrected. High-resolution mass spectral analysis (HRMS) data were recorded by Electronic Ionization (EI).

4.2. General procedure for preparation of compounds 2, 5, and 7

Carbonyl compounds **1**, **4**, or **6** (0.2 mmol) were added to a solution of TEMPO (38 mg, 0.24 mmol) in CH_3CN (2.0 mL) at room temperature, and the mixture was stirred for 5 min. DDQ (50 mg, 0.22 mmol) was added to the mixture, which was stirred under the same conditions until the reaction was complete as judged by TLC. (For preparation of quinoxaline derivative **5**, *o*-diaminobenzene (46 mg, 0.4 mmol), and *p*-toluenesulfonic acid (12 mg, 0.06 mmol) were added to resulting mixture, which was stirred under reflux for additional 1 h.) The resulting mixture was then purified by column chromatography on 100–200 mesh silica gel to afford pure compounds **2**, **5** or **7**. And as reported in literature, the spectra of both ^1H and ^{13}C NMR of compounds **2** clearly show the mixture of VTC and its hydrated form in varied ratio.

4.3. Characterization data of products

*4.3.1. Compound **2a**.*[17] A yellowish viscous oil (8 h, 92%, yield). Mixture of ketone and corresponding hydrated form in ratio of 1:3. R_f=0.23 (petroleum ether/ethyl acetate=4:1). Ketone: ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J=7.7 Hz, 2H), 7.68 (t, J=7.4 Hz, 1H), 7.52 (t, J=7.5 Hz, 2H), 4.40 (q, J=7.1 Hz, 2H), 1.35 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 183.8, 160.5, 135.6, 131.5, 130.0, 129.2, 63.4, 13.9. Hydrate: ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J=7.8 Hz, 2H), 7.59 (t, J=7.4 Hz, 1H), 7.44 (t, J=7.5 Hz, 2H), 5.54 (s, 2H), 4.18 (q, J=7.1 Hz, 2H), 1.04 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 169.9, 134.6, 131.4, 130.2, 128.8, 91.8, 63.1, 13.6.

*4.3.2. Compound **2b**.*[9o] A yellowish oil (8 h, 90%, yield). Mixture of ketone and corresponding hydrated form in ratio of 1:3. R_f=0.25 (petroleum ether/ethyl acetate=4:1). Ketone: ^1H NMR (400 MHz, $CDCl_3$) δ 8.01–7.96 (m, 2H), 7.70 (t, J=7.5 Hz, 1H), 7.54 (t, J=7.8 Hz, 2H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 183.4, 160.8, 135.6, 131.4, 130.0, 129.2, 53.5. Hydrate: ^1H NMR (400 MHz, $CDCl_3$) δ 8.10–8.05 (m, 2H), 7.62 (t, J=7.4 Hz, 1H), 7.47 (t, J=7.8 Hz, 2H), 5.45 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 170.4, 134.7, 131.2, 130.2, 128.8, 91.8, 53.7.

*4.3.3. Compound **2c**.* A white solid (12 h, 90%, yield). Mixture of ketone and corresponding hydrated form in ratio of 1:3. R_f=0.30 (petroleum ether/ethyl acetate=4:1). Mp: 88–89 °C. Ketone: ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J=8.2 Hz, 2H), 7.34 (d, J=8.2 Hz, 2H), 3.95 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 183.5, 170.0, 147.1, 130.2, 129.9, 129.0, 53.4, 22.0. Hydrate: ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J=8.2 Hz, 2H), 7.27 (d, J=8.2 Hz, 2H), 5.40–5.36 (m, 2H), 3.74 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 190.8, 170.6, 146.1, 130.4, 129.6, 128.7, 91.6, 53.7, 21.9. HRMS(EI) calcd for $C_{11}H_{10}O_4$ $[M]^+$ 206.0579, found: 206.0575.

4.3.4. Compound ***2d***.[9o] A yellowish solid (8 h, 64%, yield). Mixture of ketone and corresponding hydrated form in ratio of 1:5. R_f=0.25 (petroleum ether/ethyl acetate=4:1). Mp: 81–83 °C. Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J*=9.0 Hz, 2H), 6.99 (d, *J*=9.0 Hz, 2H), 3.93 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 183.6, 165.6, 161.2, 132.7, 124.5, 114.6, 55.7, 53.4. Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J*=9.0 Hz, 2H), 6.92 (d, *J*=9.0 Hz, 2H), 5.56 (s, 2H), 3.86 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 170.7, 164.8, 132.9, 124.0, 114.2, 91.6, 55.6, 53.6.

4.3.5. Compound ***2e***. A white solid (9 h, 85%, yield). Mixture of ketone and corresponding hydrated form in ratio of 1:7. R_f=0.20 (petroleum ether/ethyl acetate=4:1). Mp: 86–88 °C. Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*=8.7 Hz, 2H), 7.53 (d, *J*=8.7 Hz, 2H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 182.8, 160.9, 142.5, 131.6, 131.4, 128.8, 53.6. Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J*=8.7 Hz, 2H), 7.46 (d, *J*=8.7 Hz, 2H), 5.34 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 170.2, 141.5, 131.6, 129.6, 129.3, 91.8, 53.8. HRMS(EI) calcd for $C_{10}H_7ClO_4$ $[M]^+$ 226.0033, found: 226.0026.

4.3.6. Compound ***2f***.[9o] A white solid (8 h, 64%, yield). Mixture of ketone and corresponding hydrated form in ratio of 1:10. R_f=0.20 (petroleum ether/ethyl acetate=4:1). Mp: 86–88 °C. Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J*=8.6 Hz, 2H), 7.69 (d, *J*=8.6 Hz, 2H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 182.0, 160.1, 132.6, 131.4, 53.6. Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J*=8.7 Hz, 2H), 7.62 (d, *J*=8.7 Hz, 2H), 5.40 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 170.1, 132.3, 131.6, 130.4, 130.0, 91.8, 53.8.

4.3.7. Compound ***2g***. A white solid (8 h, 77%, yield). Mixture of ketone and corresponding hydrated form in ratio of 1:10. R_f=0.20 (petroleum ether/ethyl acetate=4:1). Mp: 75–77 °C. Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (t, *J*=1.7 Hz, 1H), 7.92–7.89 (m, 1H), 7.81 (ddd, *J*=8.0, 1.9, 1.0 Hz, 1H), 7.41 (t, *J*=7.9 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 182.6, 160.7, 138.4, 133.1, 132.6, 130.7, 128.7, 123.4, 53.7. Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (t, *J*=1.8 Hz, 1H), 8.00–7.98 (m, 1H), 7.73 (ddd, *J*=8.0, 1.9, 1.0 Hz, 1H), 7.33 (t, *J*=7.9 Hz, 1H), 5.51 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 169.9, 137.5, 133.1, 133.0, 130.4, 128.8, 123.1, 92.0, 53.8. HRMS(EI) calcd for $C_{10}H_7BrO_4$ $[M]^+$ 269.9528, found: 269.9524.

4.3.8. Compound ***2h***. A yellowish solid (9 h, 88%, yield). Mixture of ketone and corresponding hydrated form in ratio of 1:6. R_f=0.20 (petroleum ether/ethyl acetate=2:1). Mp: 94–96 °C. Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.04 (dd, *J*=8.7, 1.7 Hz, 1H), 7.96–7.94 (m, 2H), 7.87–7.85 (m, 1H), 7.70–7.52 (m, 2H), 3.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 183.5, 161.0, 136.7, 134.0, 132.3, 130.1, 130.0, 129.4, 128.8, 128.0, 127.4, 123.5, 53.6. Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.09 (dd, *J*=8.7, 1.7 Hz, 1H), 7.96 (d, *J*=6.7 Hz, 1H), 7.90–7.85 (m, 2H), 7.70–7.52 (m, 2H), 5.59 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 170.6, 136.2, 133.1, 132.3, 130.2, 129.5, 128.7, 128.6, 127.8, 127.1, 124.8, 92.0, 53.8. HRMS(EI) calcd for $C_{14}H_{10}O_4$ $[M]^+$ 242.0579, found: 242.0576.

4.3.9. Compound ***2i***. A yellowish solid (12 h, 87%, yield). Mixture of ketone and corresponding hydrated form in ratio of 1:6. R_f=0.15 (petroleum ether/ethyl acetate=3:1). Mp: 72–74 °C. Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J*=3.9, 1.0 Hz, 1H), 7.89 (dd, *J*=4.9, 1.1 Hz, 1H), 7.21 (dd, *J*=4.8, 4.1 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.0, 179.6, 161.8, 138.6, 137.8, 137.3, 129.2, 53.4. Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J*=3.9, 1.1 Hz, 1H), 7.76 (dd, *J*=4.9, 1.0 Hz, 1H), 7.13 (dd, *J*=4.7, 4.1 Hz, 1H), 5.54 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9, 170.2, 136.9, 136.8, 136.6, 128.8, 92.3, 53.9. HRMS(EI) calcd for $C_8H_6O_4S$ $[M]^+$ 197.9987, found: 197.9982.

4.3.10. Compound ***2j***. A yellowish solid (12 h, 46%, yield). Mixture of ketone and corresponding hydrated form in ratio of 1:10. R_f=0.15 (petroleum ether/ethyl acetate=3:1). Mp: 86–88 °C. Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J*=4.2 Hz, 1H), 7.07 (d, *J*=4.2 Hz, 1H), 3.97 (s, 3H). Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J*=4.2 Hz, 1H), 6.99 (d, *J*=4.2 Hz, 1H), 7.12–7.14 (m, 1H), 5.30 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.9, 169.9, 142.9, 136.3, 135.2, 128.3, 92.1, 54.0. HRMS(EI) calcd for $C_8H_5ClO_4S$ $[M]^+$ 231.9597, found: 231.9596.

4.3.11. Compound ***2k***.[17] A yellowish oil (8 h, 65%, yield). Mixture of ketone and corresponding hydrated form in ratio of 1:3. R_f=0.20 (petroleum ether/ethyl acetate=4:1). Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J*=7.0, 1.5 Hz, 2H), 7.71–7.66 (m, 1H), 7.54–7.52 (m, 2H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 193.6, 187.2, 135.4, 132.1, 129.6, 129.3, 24.7. Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J*=7.0, 1.5 Hz, 2H), 7.65–7.59 (m, 1H), 7.49–7.44 (m, 2H), 5.57 (s, 2H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 193.4, 135.0, 131.5, 130.4, 129.1, 95.1, 23.8.

4.3.12. Compound ***2l***.[10c] A yellowish solid (16 h, 92%, yield). Mixture of ketone and corresponding hydrated form in ratio of 10:1. R_f=0.25 (petroleum ether/ethyl acetate=6:1). Mp: 71–73 °C. Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.06 (m, 4H), 7.76–7.67 (m, 2H), 7.59–7.51 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 188.3, 135.4, 132.1, 130.2, 129.1. Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.92 (m, 4H), 7.56–7.47 (m, 2H), 7.39–7.31 (m, 4H), 5.96 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 134.6, 132.0, 130.2, 128.8, 94.1.

4.3.13. Compound ***2m***.[18] A yellowish oil (9 h, 55%, yield). Mixture of ketone and corresponding hydrated form in ratio of 5:2. R_f=0.22 (petroleum ether/ethyl acetate=6:1). Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–8.00 (m, 2H), 7.69–7.63 (m, 1H), 7.51 (t, *J*=7.8 Hz, 2H), 3.14 (s, 3H), 3.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 185.6, 165.5, 135.2, 131.9, 130.3, 128.9, 36.9, 34.5. Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–8.00 (m, 2H), 7.62–7.57 (m, 1H), 7.44 (t, *J*=7.8 Hz, 2H), 6.00 (s, 2H), 2.97 (s, 3H), 2.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 168.7, 134.7, 131.8, 130.0, 128.9, 91.3, 37.4, 37.0.

4.3.14. Compound ***2n***.[17] A yellowish oil (16 h, 80%, yield). Mixture of ketone and corresponding hydrated form in ratio of 4:3. R_f=0.15 (petroleum ether/ethyl acetate=3:1). Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.83 (m, 2H), 7.66–7.61 (m, 1H), 7.56–7.49 (m, 2H), 7.14 (s, 1H), 3.41–3.32 (m, 2H), 1.19 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 188.9, 159.2, 135.3, 134.4, 129.5, 129.1, 34.5, 14.3. Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–8.08 (m, 2H), 7.57–7.52 (m, 1H), 7.42–7.37 (m, 2H), 6.68 (s, 1H), 5.86 (s, 2H), 3.26–3.18 (m, 2H), 1.02 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 169.1, 132.1, 131.6, 130.5, 128.5, 93.2, 35.1, 14.2.

4.3.15. Compound ***3***.[15] A colorless oil (8 h, 35%, yield). R_f=0.25 (petroleum ether/ethyl acetate=20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J*=7.5 Hz, 2H), 7.56 (t, *J*=7.4 Hz, 1H), 7.45 (t, *J*=7.7 Hz, 2H), 5.40 (s, 1H), 4.15 (m, 2H), 1.47–1.28 (m, 9H), 1.15 (m, 6H), 0.98 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 168.2, 134.5, 133.7, 129.8, 128.5, 92.9, 61.7, 60.5, 60.0, 40.2, 40.0, 33.2, 32.5, 20.2, 20.2, 17.0, 14.0.

4.3.16. Compound ***5***. A yellowish oil (53%, yield). R_f=0.30 (petroleum ether/ethyl acetate=20:1). ^{1}H NMR (400 MHz, CDCl3) δ 8.17 (dd, *J*=8.3, 1.0 Hz, 1H), 8.07 (dd, *J*=8.4, 1.0 Hz, 1H), 7.85–7.80 (m, 1H), 7.78–7.73 (m, 1H), 5.46–5.35 (m, 2H), 4.07 (s, 3H), 3.29–3.23 (m, 2H), 2.20 (q, *J*=6.8 Hz, 2H), 2.09–2.01 (m, 2H), 1.94–1.86

(m, 2H), 0.96 (t, J=7.5 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 166.1, 156.3, 144.1, 142.7, 139.7, 132.5, 131.7, 129.9, 129.7, 128.7, 128.3, 53.2, 35.6, 29.2, 27.0, 20.6, 14.3. HRMS(EI) calcd for $C_{17}H_{20}N_2O_2$ $[M]^+$ 284.1525, found: 284.1523.

4.3.17. Compound ***7a***. A colorless oil (12 h, 49%, yield). R_f=0.30 (petroleum ether/ethyl acetate=10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J=7.8 Hz, 2H), 7.63 (t, J=7.3 Hz, 1H), 7.52 (t, J=7.5 Hz, 2H), 6.19 (s, 1H), 3.08 (s, 3H), 1.60–1.24 (m, 12H), 1.15 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 136.8, 134.2, 129.9, 129.1, 128.9, 128.6, 95.3, 56.3, 40.9, 40.7, 40.1, 37.6, 34.7, 27.3, 20.3, 16.7, 16.4. HRMS(EI) calcd for $C_{18}H_{27}NO_4S$ $[M]^+$ 353.1661, found: 353.1664.

4.3.18. Compound ***7b***.[15] A colorless oil (12 h, 58%, yield). R_f=0.20 (petroleum ether/ethyl acetate=50:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J=7.8 Hz, 2H), 7.64 (t, J=7.3 Hz, 1H), 7.50 (t, J=7.6 Hz, 2H), 6.52 (s, 1H), 1.65–1.27 (m, 9H), 1.08 (s, 6H), 0.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 134.8, 132.4, 130.1, 128.9, 115.1, 56.8, 40.3, 39.8, 35.0, 32.9, 32.2, 31.8, 27.5, 20.5, 16.8.

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