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An entry to polysubstituted furans via the oxidative ring opening of furan ring employing NBS as an oxidant

Huiyue Yu [a], Weiqiang Zhong [b], Tingyu He [a], Wenxiang Gu [a], Biaolin Yin [b,*]

[a] Department of Applied Chemistry, College of Science, South China Agricultural University, Guangzhou 510642, PR China
[b] School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou, Guangdong 510640, PR China

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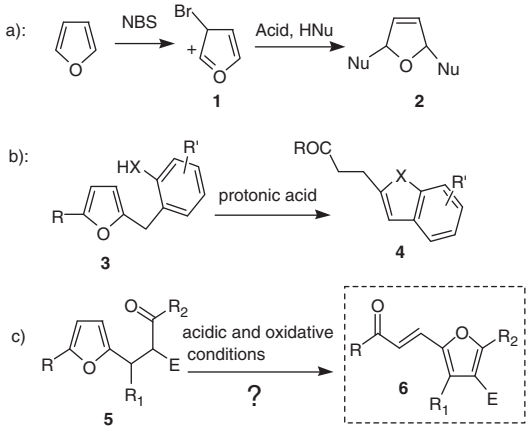
ABSTRACT

A class of polysubstituted functionalized furans was synthesized efficiently starting from readily available furans involving the oxidative ring opening of the furan rings using NBS as an oxidant. The reaction proceeded through a sequence of oxidative dearomatization of the furan ring/spirocyclization/aromatization.

The polysubstituted furans represent an important class of five-membered heterocycles found to widely exist in a number of bioactive natural products as well as in various pharmaceuticals and agrochemicals.[1] On the other hand, because furan rings can provide up to four unsaturated carbons and contain masked functionalities of olefin, diene, enol ether, and 1,4-dicarbonyl, these polysubstituted furans also represent valuable synthetic intermediates for the preparation of a series of important molecules. To date, there are a number of different methods that, despite having unequal scope, allow the dearomatization of the furan ring.[2] For example, the Birch-reduction of furan rings results in 2,5-dihydrofurans,[3] while cycloadditions of furans as dienes have been widely used for the construction of different bicyclic or tricyclic skeletons.[4] Likewise, 2-furycarbinols are isomerized into cyclopentenones upon treatment with acids in aqueous media.[5] For these reasons, the synthesis of polysubstituted furan and work toward developing new synthetic methods using furans as the fundamental building blocks continue to attract the interest of many synthetic chemists. Nevertheless, the development of a flexible and predictable approach to polysubstituted furans starting from inexpensive and readily available furans via the ring opening of the furan ring has seldom been reported.[6]

Due to the high electron-density of the furan ring, its dearomatizing oxidation is easily achieved by using a range of oxidants such as O_2, Br_2, NBS, *m*-CPBA, and so on, to construct complex molecules.[7] For example, the well-known NBS-mediated oxidation of furan rings begins with an electrophilic bromination of the furan ring, thus revealing an electrophilic oxonium ion **1** (Scheme 1a). Trapping of the oxonium ion **1** with nucleophiles leads to the production of 2,5-dihydrofurans. This strategy has been successfully applied to the synthesis of trioxadispiroketals from furans carrying two nucleophilic side chains at the two α-positions.[8] Recently, a general approach to the synthesis of benzoannelated heterocyclic compounds was developed based on the cyclization of *ortho*-substituted benzylfurans under acidic conditions (Scheme 1b).[9] This method involved the acetalization step using the furan ring



Scheme 1. Strategy to polysubstituted furans **6**.

* Corresponding author. Tel./fax: +86 20 87113735.
E-mail address: blyin@scut.edu.cn (B. Yin).

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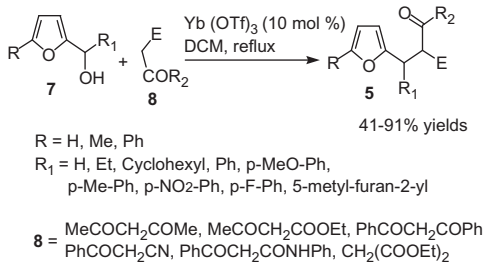
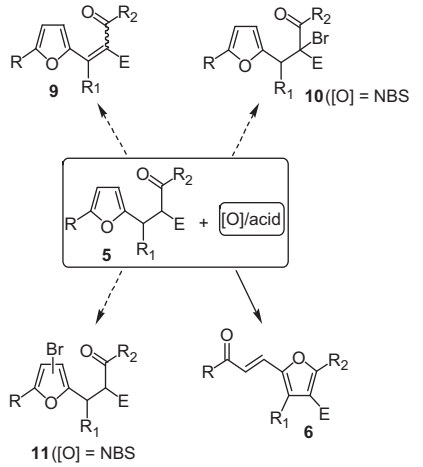


Scheme 2. The synthesis of the precursors **5** for recyclization.

as the source of carbonyl group and a subsequent aromatizing ring-opening step. Inspired by these two reactions, we further considered the fact that chemical properties of the enolic hydroxyl group are similar to those of the phenolic group. Working from this idea, we envisioned that a general method for the synthesis of polysubstituted furans **6** from furans **5** could be developed under both acidic and oxidative reaction conditions. With our interest in the synthesis of heterocyclic compounds based on the dearomatization of the furan ring,[10,11] we herein discuss a practical and concise route to synthesizing both polysubstituted and functionalized furans from furans via the acid-catalyzed oxidative ring opening of the furan ring.

At the outset of this study, the precursors **5** were prepared via the reaction of 2-furylcarbinols **7** with activated methylene compounds **8** in DCM in the presence of $Yb(OTf)_3$ (10 mol %) as the catalyst (Scheme 2). The success of the cyclization of **5** into **6** relies on the careful selection of the substrate **5,** followed by choosing the suitable reaction conditions to suppress the direct dehydrogenation of **5** to form α,β-unsaturated carbonyl compound **9**, the bromination of the α-position of the carbonyl group to form side product **10**, and the direct bromination of the furan ring to form side product **11** (Scheme 3). With these considerations, furan **5a** was used as the substrate under the influence of various Lewis acids and oxidants to optimize the reaction conditions, with results summarized in Table 1. Initially, **5a** was treated with a series of oxidants such as $PhI(OAc)_2$, *m*-CPBA, Br_2, Ag_2CO_3, and BQ in the presence of AcOH in DCE. It was found that these systems were not suitable for this conversion and none of the product **6a** was observed (entries 1–5). Specifically, $PhI(OAc)_2$ resulted in the formation of **10a** exclusively (entry 1). The oxidants of *m*-CPBA, Br_2, and BQ (benzoquinone) produced complicated reaction systems



Scheme 3. Potential challenging for the oxidative recyclization of **5** into **6.**

Table 1
Optimization of the reaction conditions[a,b,c]

Entry	Conditions	Yield[d] (%)
1	$AcOH/PhI(OAc)_2$ /DCE/rt, 3 h	ND[e]
2	AcOH/*m*-CPBA/DCE/rt, 3 h	ND
3	$AcOH/Br_2$/DCE, rt, 3 h	ND
4	AcOH/BQ/DCE, rt, 3 h	ND
5	$AcOH/Ag_2CO_3$/DCE, 100 °C, 24 h	NR[f]
6	AcOH/NBS/DCE, rt, 0.5 h/100 °C 20 h	Trace
7	$AcOH/NBS/THF-H_2O$, rt, 0.5 h/80 °C, 15 h	41
8	$PTSA/NBS/THF-H_2O$, rt, 0.5 h/80 °C, 20 h	61
9	$AgF/NBS/THF-H_2O$, rt, 0.5 h/80 °C, 15 h	58
10	$PPTS/NBS/THF-H_2O$, rt, 0.5 h/80 °C, 24 h	51
11	$Cu(OTf)_2$/AcOH/NBS/$THF-H_2O$, rt, 0.5 h/80 °C, 24 h	61
12	**$Cu(OAc)_2$/AcOH/ NBS/$THF-H_2O$, rt, 0.5 h/80 °C, 15 h**	**71**
13	$FeCl_2/NBS/THF-H_2O$, rt, 0.5 h/80 °C, 10 h	63
14	$ZnCl_2/NBS/THF-H_2O$, rt, 0.5 h/80 °C, 10 h	54
15	$FeCl_3/NBS/THF-H_2O$, rt, 0.5 h/80 °C, 10 h	55
16	$Cu(OAc)_2$/NBS/THF, rt, 0.5 h/then 80 °C, 10 h	21
17	$Cu(OAc)_2$/AcOH/NBS/MeCN, rt, 0.5 h/80 °C, 3 h	38

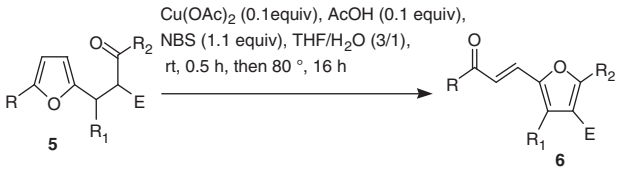
[a] All reactions were carried out on a 0.3 mmol scale.
[b] Unless otherwise noted, 0.1 equiv of the acid and 1.1 equiv of the oxidant were used.
[c] $V(THF)/V(H_2O) = 3/1$.
[d] Isolated yield.
[e] ND: not detected.
[f] NR: no reaction.

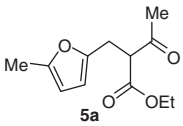
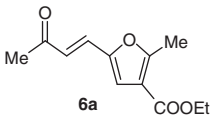
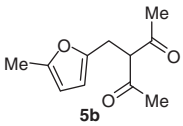
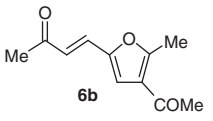
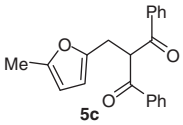
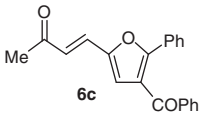
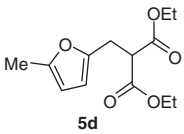
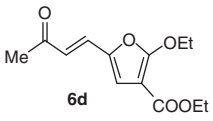
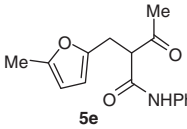
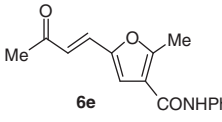
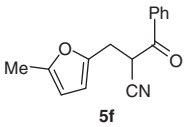
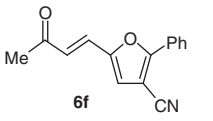
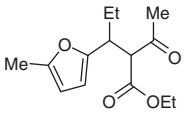
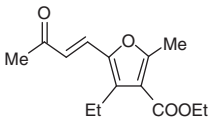
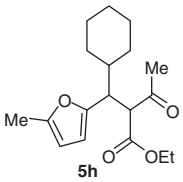
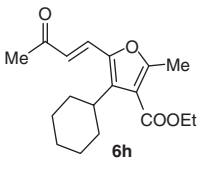
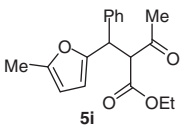
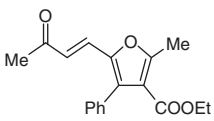
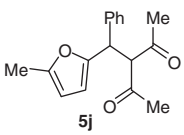
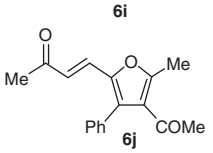
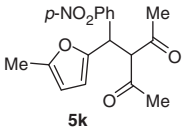
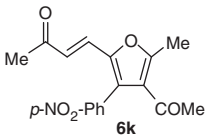
(entries 2–4). The weak oxidant Ag_2CO_3 gave rise to no reaction (entry 5). Treatment of **5a** with NBS (1.1 equiv) in the presence of 0.1 equiv of acetic acid in DCE at room temperature produced a new and unstable compound with a larger polarity than **5a** according to the TLC. After about 0.5 h, the starting material **5a** had been consumed completely. Heating the reaction mixture at 110 °C for 20 h produced a trace amount of **6a** (entry 6). When the solvent was switched to THF/H_2O (3/1), the reaction of **5a** with NBS at room temperature also produced the same unstable compound as that in DCE. After heating the resulting reaction mixture at 80 °C for 15 h, **6a** was formed in 41% yield (entry 7). Encouraged by this outcome, we examined different acids and found that $Cu(OAc)_2$ (0.1 equiv)/AcOH (0.1 equiv) system was proved to be the best, giving rise to **6a** in 71% yield (entries 8–15). Notably, when anhydrous THF or MeCN was used as the solvent, the yields were less than 40% and a considerable amount of by-product **11a** was produced (entries 16 and 17). We conjectured that using H_2O as the solvent would be helpful in dissolving of the acids and facilitating the opening of the furan ring.

With the optimized reaction conditions in hand, a variety of furans **5** with different R, R_1, R_2, and E groups were tested to investigate the reaction scope.[12] Results of this effort are provided in Table 2. When R_2 was a Me or Ph group, and E was an electron-withdrawing group such as acetyl, benzoyl, and ethoxyacyl, these reactions tend to proceed smoothly. The desired **6** was produced in moderate to good yields. (entries 1–3). Due to the formation of a certain amount of by-product **9c**, the yield of **6c** was relative low (45%). The failure of **5d**–**5f** could be attributed to the low acidity of the proton of the activated methylene group which led to the low concentration of enol under these reaction conditions. The scope of R_1 group was then tested. We were delighted to find that a series of **6** were produced in moderate to good yields with a variable R_1 group including alkyl, hetero-aryl, and phenyl groups with electron-donating or electron-withdrawing substituents. The lower yield of **6l** might result from the sterically bulky R_2 group, which has a tendency to impede attacking of the carbonyl group on the α-position of the furan ring. The reaction system of **5r** showed to be relatively complicated due to the instability of the furan ring in acidic system, thus leading to a very low yield of **6r** (28%).

Based on the experimental results shown above, a tentative mechanism for the synthesis of **6** was proposed in Scheme 4.

Table 2
The synthesis of **6**[a]



Entry	5	6	Yield[b] (%)
1			70
2			75
3			45
4			ND
5			ND
6			ND
7			36
8			41
9			58
10			62
11			65

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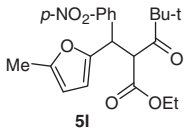
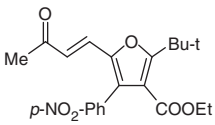
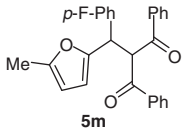
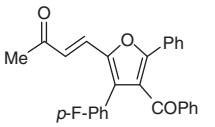
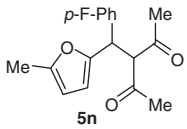
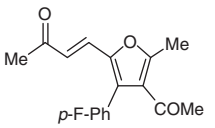
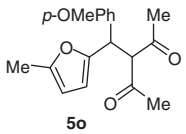
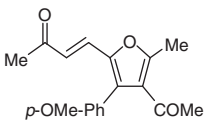
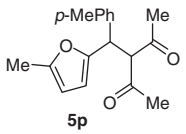
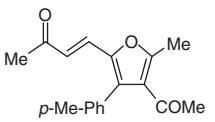
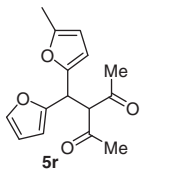
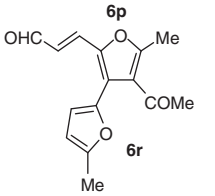
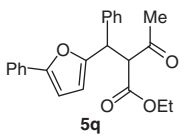
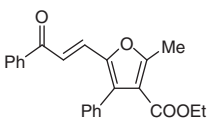
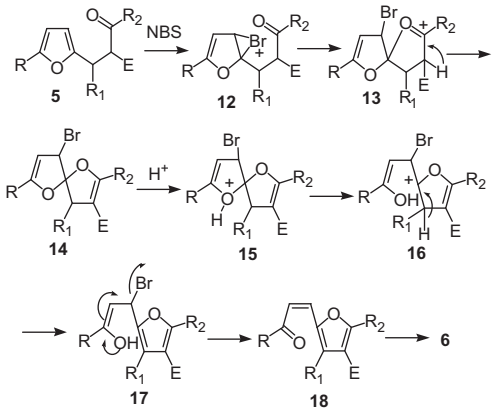
12			31
13			60
14			74
15			75
16			72
17			28
18			57

[a] All reactions were carried out on a 0.3 mmol scale.
[b] Isolated yield.

Initially, NBS oxidation of the double bond of the furan ring of **5** resulted in the bromonium ion **12**. The ring opening of the bromonium ion with the intramolecular carbonyl group led to the intermediate **13**, which was deprotonated to **14**. Compound **14** then underwent protonation and the subsequent ring opening step to produce the carbocation **16**. Compound **16** was finally transformed into **6** through three successive steps of deprotonation, elimination of HBr, and geometric isomerization of the double bond.

In summary, we have developed a practical method for the preparation of polysubstituted and functionalized furans. This method is based on the oxidative ring opening of the furan rings using NBS as the oxidant. The reaction proceeded through a sequence of oxidative dearomatization of the furan ring/spirocyclization/aromatization. This protocol possesses the advantages of readily available starting materials, mild reaction conditions, and short steps. Further studies on the synthesis of polysubstituted and functionalized thiophenes and pyrroles using this protocol are under way in our laboratory and the results will be reported in due course.



Scheme 4. The proposed mechanism for the formation of **6.**

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.085.

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12. *Typical procedure for the synthesis of* ***6:*** To a 25 mL flask was added **5** (0.3 mmol, 1 equiv), THF (3 mL), H_2O (1 mL), AcOH (0.03 mmol, 0.1 equiv), and NBS (0.33 mmol, 1.1 equiv). The mixture was stirred for 30 min at room temperature until the disappearance of **5** according to the TLC. The reaction mixture then was heated to 80 °C for 15 h. After cooled to room temperature, the reaction mixture was added saturated $Na_2S_2O_3$ solution (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography to afford **6**.
Compound ***6a****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 15.9 Hz, 1H), 6.88 (s, 1H), 6.58 (d, J = 15.9 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.61 (s, 3H), 2.31 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 163.1, 161.6, 148.5, 128.6, 124.4, 116.4, 116.1, 60.4, 28.0, 14.3, 14.1.
Compound ***6b****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 15.9 Hz, 1H), 6.87 (s, 1H), 6.62 (d, J = 15.9 Hz, 1H), 2.65 (s, 3H), 2.43 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 193.3, 161.0, 148.5, 128.4, 124.6, 123.7, 115.5, 29.0, 28.0, 14.6.
Compound ***6c****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.5 Hz, 2H), 7.75 (dd, J = 6.4, 2.9 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.37–7.30 (m, 3H), 7.27 (d, J = 4.9 Hz, 1H), 6.92 (s, 1H), 6.77 (d, J = 15.9 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 190.9, 157.3, 149.1, 137.5, 133.35, 129.9, 129.7, 128.9, 128.5, 128.4, 127.7, 126.9, 125.5, 123.2, 118.6, 28.0.
Compound ***6g****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.20 (m, 1H), 6.56 (d, J = 15.6 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.72 (q, J = 7.4 Hz, 2H), 2.57 (s, 3H), 2.29 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 163.5, 162.0, 145.0, 134.0, 126.3, 122.4, 115.2,, 60.2, 28.4, 17.8, 15.4, 14.6, 14.1.
Compound ***6h****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 15.5 Hz, 1H), 6.58 (d, J = 15.5 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.19–3.02 (m, 1H), 2.54 (s, 3H), 2.31 (s, 3H), 1.84–1.68 (m, 7H), 1.43–1.29 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 163.9, 161.4, 144.8, 136.8, 128.1, 122.6, 115.5, 60.3, 35.8, 32.6, 28.6, 27.0, 25.9, 14.9.
Compound ***6i****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.37 (m, 3H), 7.30–7.26 (m, 2H), 7.07 (d, J = 15.9 Hz, 1H), 6.65 (d, J = 15.9 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.67 (s, 3H), 2.24 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 163.2, 161.5, 146.0, 131.8, 131.1, 130.0, 128.1, 127.9, 127.6, 124.5, 115.7, 60.2, 28.0, 14.5, 13.8.
Compound ***6j****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 6.6 Hz, 3H), 7.25 (dd, J = 7.6, 2.0 Hz, 2H), 6.99 (d, J = 15.8 Hz, 1H), 6.63 (d, J = 15.8 Hz, 1H), 2.60 (s, 3H), 2.21 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 195.2, 160.4, 145.8, 131.4, 130.9, 129.7, 128.8, 128.7, 127.3, 124.7, 124.5, 30.7, 28.2, 14.6.
Compound ***6k****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 15.7 Hz, 1H), 6.70 (d, J = 15.7 Hz, 1H), 2.65 (s, 3H), 2.25 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2, 193.7, 160.6, 147.8, 146.2, 138.4, 130.8, 128.4, 126.0, 125.7, 124.3, 123.8, 30.8, 28.5, 14.9.
Compound ***6l****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 15.8 Hz, 1H), 6.69 (d, J = 15.8 Hz, 1H), 4.15–4.09 (m, 2H), 2.28 (s, 3H), 1.47 (s, 9H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2, 167.5, 163.8, 147.6, 144.7, 138.4, 130.5, 129.6, 128.8, 126.4, 125.7, 123.5, 123.3, 115.6, 61.2, 35.1, 28.5, 28.3, 13.7.
Compound ***6m****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.3 Hz, 2H), 7.64 (dd, J = 6.6, 2.9 Hz, 2H), 7.44 (t, J = 7.4 Hz, 1H), 7.36–7.19 (m, 8H), 6.99 (t, J = 8.6 Hz, 2H), 6.90 (d, J = 15.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 192.5, 164.0, 161.5, 153.92, 146.3, 136.8, 133.9, 132.1, 131.2, 131.2, 129.7, 129.7, 128.8, 128.6, 128.6, 127.1, 126.8, 126.4, 125.5, 123.3, 116.0, 115.8, 28.3.
Compound ***6n****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 2H), 7.17 (t, J = 8.6 Hz, 2H), 6.99 (d, J = 15.8 Hz, 1H), 6.67 (d, J = 15.8 Hz, 1H), 2.64 (s, 3H), 2.26 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 194.8, 164.2, 161.7, 160.5, 146.0, 131.6, 131.5, 129.7, 127.4, 127.4, 126.9, 124.7, 124.6, 116.0, 115.8, 30.8, 28.3, 14.7.
Compound ***6o****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 15.8 Hz, 1H), 6.97 (d, J = 8.7 Hz, 2H), 6.62 (d, J = 15.8 Hz, 1H), 3.85 (s, 3H), 2.60 (s, 3H), 2.23 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.45, 195.39, 160.33, 159.90, 145.82, 130.91, 130.77, 127.43, 124.74, 124.16, 123.39, 114.26, 55.29, 30.69, 28.16, 14.63.
Compound ***6p****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (q, J = 8.0 Hz, 4H), 7.08 (d, J = 15.9 Hz, 1H), 6.63 (d, J = 15.9 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 2.66 (s, 3H), 2.39 (s, 3H), 2.24 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 163.2, 161.4, 146.0, 137.9, 132.0, 129.9, 128.6, 128.0, 127.8, 124.3, 115.7, 60.2, 27.9, 21.2, 14.5, 13.9.

Compound ***6r****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 15.6 Hz, 1H), 6.63 (dd, J = 15.7, 7.9 Hz, 1H), 6.51 (d, J = 3.1 Hz, 1H), 6.15 (d, J = 3.2 Hz, 1H), 2.60 (s, 3H), 2.38 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.0, 192.6, 160.9, 154.2, 145.8, 142.2, 135.8, 126.6, 123.7, 123.0, 121.3, 113.4, 107.9, 30.0, 14.6, 13.7.

Compound ***6q****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.2 Hz, 2H), 7.56–7.31 (m, 10H), 4.15 (q, J = 7.1 Hz, 2H), 2.72 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.3, 163.3, 161.5, 146.9, 138.2, 132.71, 132.2, 131.1, 130.1, 129.1, 128.5, 128.3, 128.1, 127.9, 119.4, 115.9, 60.2, 14.6, 13.8.