Tetrahedron 67 (2011) 3010–3016

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of new aryl substituted furan-2(5*H*)-ones using the Suzuki–Miyaura reaction

Ruonan Zhang [a], George Iskander [a], Paulo da Silva [a], Daniel Chan [a], Valentina Vignevich [a], Vi Nguyen [a], Mohan M. Bhadbhade [b], David StC Black [a], Naresh Kumar [a,*]

[a] School of Chemistry, The University of New South Wales, Sydney, NSW 2052, Australia
[b] Analytical Centre, The University of New South Wales, Sydney, NSW 2052, Australia

ARTICLE INFO

Article history:
Received 5 November 2010
Received in revised form 24 January 2011
Accepted 7 February 2011
Available online 19 February 2011

Keywords:
Furanone
Suzuki–Miyaura
Fimbrolide
Antibacterial

ABSTRACT

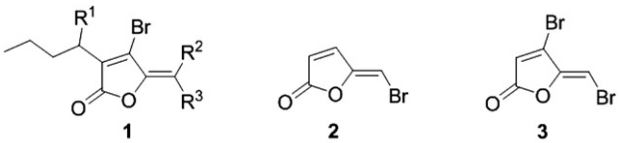
A series of novel 5-arylidenefuran-2(5*H*)-ones and 5-arylidene-4-arylfuran-2(5*H*)-ones were synthesized via the Suzuki–Miyaura reactions of fimbrolide derivatives 5-(bromomethylene)furan-2(5*H*)-one and 4-bromo-5-(bromomethylene)furan-2(5*H*)-one, respectively. A regioselective Suzuki–Miyaura reaction on 4-bromo-5-(bromomethylene)furan-2(5*H*)-one allowed the synthesis of unsymmetrically substituted 5-arylidene-4-arylfuran-2(5*H*)-ones. The crystal structure of the intermediate 5-arylidene-4-bromofuran-2(5*H*)-one revealed interesting Br···O halogen bonding.

1. Introduction

Since the discovery of penicillin in 1928, antibiotics have been heavily and often indiscriminately employed to combat microbial infections. Our overreliance on conventional antibiotics has driven the emergence of multidrug resistance in bacteria, which is posing a serious threat to human health.[1] Methicillin-resistant *Staphylococcus aureus* (MRSA), a feared 'superbug', that is, resistant to most antibiotics, is a major cause of nosocomial infections worldwide. There is thus an urgent need for the development of new therapeutic compounds with novel modes of action to supplement existing anti-microbials.[2] Recent research into the various regulatory systems in bacteria that control the expression of biofilm formation and virulence factors have identified new targets for potential therapeutic intervention.

Quorum sensing is an intricate communication system employed by bacteria that utilizes small intercellular diffusible chemicals as signaling compounds to communicate with each other.[3] These molecules, such as *N*-acyl-L-homoserine lactones (AHL) employed by pathogenic gram-negative bacteria species, regulate bacterial biofilm formation and the expression of virulent phenotypes.[4] Bacteria in biofilms may be hundreds or up to one thousand times more resistant to antibiotics compared to bacteria in suspension.[5] Inhibiting the quorum system may therefore be an effective approach to eradicating infections without imposing the selective pressure on bacteria to develop resistance.[6]

Natural furanones **1** isolated from the red alga *Delisea pulchra* were found to possess significant inhibitory activity against bacterial quorum sensing (Fig. 1).[7] These brominated furanones or 'fimbrolides' share a common 4-halo-3-butyl-5-halomethylenefuran-2(5*H*)-one core but differ in the number and nature of the halogen substituents and the presence or absence of oxygen functionality in the butyl side-chain. These compounds interfere with AHL-mediated quorum sensing, inhibiting biofilm formation and the expression of the virulent phenotypes at non- bactericidal concentrations.[8–11] Theoretically, these furanones should not impose the same selective pressure as conventional antibiotics on bacterial strains to induce drug resistance. Over 200 analogues of furanones with different bromination patterns



R^1 = H, OH, OAc
R^2 = H, Cl, Br, I
R^3 = H, Cl, Br, I

Fig. 1. Natural fimbrolides **1** and synthetic fimbrolides **2** and **3**.

* Corresponding author. Tel.: +61 2 9385 4698; fax: +61 2 9385 6141; e-mail address: n.kumar@unsw.edu.au (N. Kumar).

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doi:10.1016/j.tet.2011.02.014

and alkyl chain lengths have been synthesized and evaluated for quorum sensing inhibitor activities.[12] Interestingly, simple furanones, such as **2** and **3** lacking the C3-butyl still show significant quorum sensing inhibitor activity.[9–11] Synthetic fimbrolide **3**, termed furanone C-30, was found to reduce *Pseudomonas aeruginosa* levels in the lungs by three orders of magnitude in a pulmonary mouse model.[10]

The Suzuki–Miyaura cross-coupling reaction is one of the most important carbon–carbon bond forming reactions in the arsenal of today's organic chemistry.[13] The Suzuki–Miyaura reaction has been previously employed to synthesise 3- and 4-aryl furan-2(5*H*)-ones lacking the C5 exocyclic double bond.[14,15] Our research group also applied the Suzuki–Miyaura reaction to close analogues of the natural fimbrolides.[16] The 5-arylidene and/or 4-arylfuran-2(5*H*)-one motif occurs in natural products and synthetic drugs, such as in the rubrolide antibiotics **4** and the COX-2 inhibitor rofecoxib (Vioxx) **5** (Fig. 2).

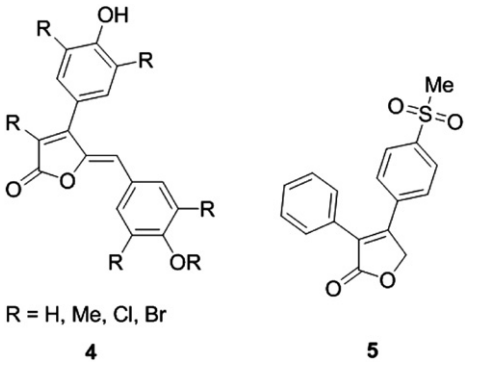


Fig. 2. The rubrolide antibiotics **4** and rofecoxib (Vioxx) **5**.

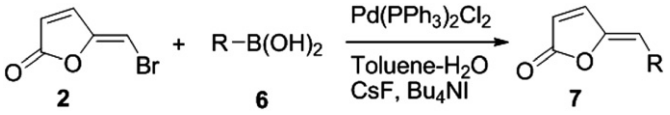
Consequently, the application of the Suzuki–Miyaura reaction to monobrominated and dibrominated fimbrolides, such as **2** and **3**, respectively, to generate new aryl substituted furanones was of high interest to us. In particular, the dihalogenated substitution pattern of fimbrolide **3** raises interesting potential issues on the chemical selectivity of the two bromine substituents and the feasibility of installing two different aryl groups on the furanone scaffold. To our knowledge, besides our preliminary report in the patent literature,[17] the Suzuki–Miyaura reactions of **2** and **3** have not yet been reported.

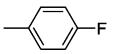
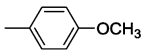
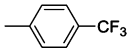
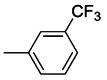
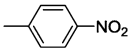
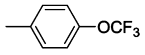
2. Results and discussion

2.1. Suzuki–Miyaura reactions of furanone 2

We started our study with investigations on the Suzuki–Miyaura reaction of known monobrominated 5-(bromomethylene)furan-2(5*H*)-one 2. Furan-2(5*H*)-one 2 has been previously subjected to the Stille reaction in the synthesis of the natural product xerulinic acid.[18–20] Compared to the Stille coupling, which uses toxic organostannane reagents, the Suzuki–Miyaura reaction is considerably milder. Diverse reaction conditions are known for the Suzuki–Miyaura reaction in the scientific literature, and are applicable to a wide variety of different organic halide and organoboron substrates. After preliminary optimization, we found that the most effective reagents for our systems used bis(triphenylphosphine) palladium(II)chloride ($Pd(PPh_3)_2Cl_2$) as the palladium catalyst, caesium fluoride (CsF) as a base and tetrabutylammonium iodide (Bu_4NI) as a phase-transfer agent in a toluene–water (1:1) biphasic solvent medium. The reactions between furanone **2** and various boronic acids **4a**–**h** were conducted at reflux for 36 h under an inert argon atmosphere. Gratifyingly, 5-arylidenefuran-2(5*H*)-ones **5a**–**h** were isolated in moderate to high yields of 74–88% (Table 1).

Table 1
Suzuki-Miyaura reactions of furanone 2



Entry	6	R	Product 7	Yield[a]
1	**6a**		**7a**	75%
2	**6b**		**7b**	80%
3	**6c**		**7c**	68%
4	**6d**		**7d**	74%
5	**6e**		**7e**	74%
6	**6f**		**7f**	75%
7	**6g**		**7g**	85%
8	**6h**		**7h**	88%

[a] Isolated yields.

We noticed that both electron-donating (e.g., entry 2) and electron-withdrawing (e.g., entries 1, 5, 7) substituents on the boronic acid substrate gave good yields. Both 2-thienyl and 3-thienyl boronic acids could be coupled with furanone **2**, albeit in slightly lower yields of 68–74%, to give 5-heteroarylidene substituted furanones. The products could be cleanly isolated as white or yellow solids after column chromatography. These conditions appear to be a general method for the installation of aryl or heteroaryl substituents at the methylene position of 5-(bromomethylene)furan-2(5*H*)-one **2**. The structure and identities of the coupling products were confirmed by ^1H and ^{13}C NMR spectroscopy as well as high-resolution mass spectrometry.

2.2. Suzuki–Miyaura reactions of furanone 3

(*Z*)-4-Bromo-5-(bromomethylene)furan-2(5*H*)-one **3** contains a bromine substituent at the C4 position as well as an exocyclic, vinylic bromine substituent. Therefore, we wished to investigate the issue of chemoselectivity of the two bromine substituents in the Suzuki–Miyaura reaction. In particular, we wished to examine whether it was possible to selectively install one aryl group while leaving the other bromine substituent untouched.

In our first attempt, we reacted furanone **3** with 2 equiv of 2,4-difluorophenylboronic acid **6j** using similar conditions as above. TLC analysis (1:1 CH_2Cl_2–hexane) of the crude product mixture revealed two closely-running spots, which were separated and subsequently determined by ^1H NMR spectroscopy to be the monoaryl substituted furanone **8a** (R_f=0.6) and the diaryl substituted furanone **9c** (R_f=0.5)

and were obtained in 24% and 27% yields, respectively. The structure of monoaryl substituted furanone **8a** was determined by 2D NMR spectroscopy. $^{1}H-^{13}C$ heteronuclear multiple bond correlation (HMBC) NMR coupling experiments revealed a strong correlation between the exocyclic vinylic proton and the C6′ proton of the aryl ring. The strong coupling suggests a 3-bond correlation that would be observed in 4-aryl substituted furanone **8a**, and not the weaker, 5-bond correlation that would be expected in the structure of 5-arylidene **8b** (Fig. 3). This result suggested that the exocyclic, vinylic bromine atom is more reactive towards the Suzuki–Miyaura reaction compared to the aromatic bromine substituent in the furanone ring. This type of selectivity has been observed previously in furanones and other heterocycles under both Suzuki and Stille coupling conditions.[20–21] Houk et al. proposes that the selectivity between the two bromines arises from differences in the bond dissociation energy and the LUMO of the heterocycle.[22]

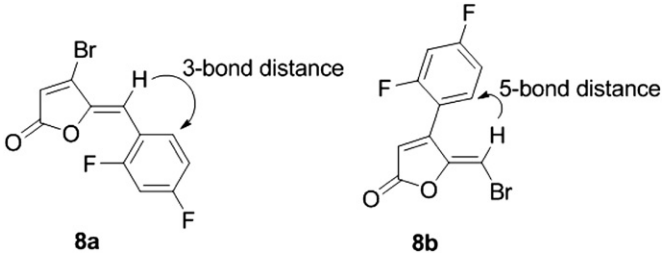
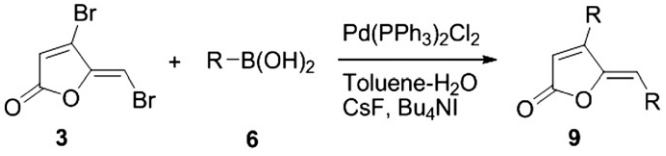
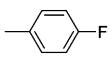
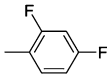
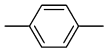
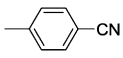


Fig. 3. Selected HMBC NMR correlations.

In order to cleanly generate disubstituted furanones containing identical aryl groups, the number of equivalents of the boronic acids was increased to 2.5. Diaryl substituted furanones **9a**–**g** were isolated as white solids or brown oils in 38–95% yields (Table 2). This methodology appears to be a general method for the synthesis

Table 2
Suzuki-Miyaura reactions of furanone 3

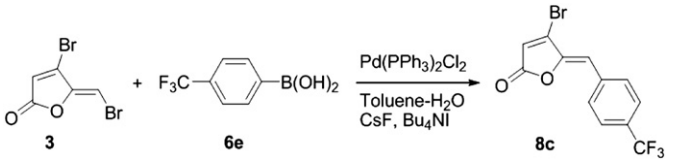


Entry	6	R	Product 9	Yield[a]
1	**6a**		**9a**	69%
2	**6i**		**9b**	88%
3	**6j**		**9c**	27%
4	**6l**		**9d**	95%
5	**6m**		**9e**	92%
6	**6n**		**9f**	64%
7	**6o**		**9g**	38%

[a] Isolated yields.

of 5-arylidene-4-arylfuran-2(5*H*)-ones that are structurally related to the naturally occurring rubrolide antibiotics **4**.

Based on the preliminary result above, we next optimized Suzuki–Miyaura reaction of dibrominated furanone **3** in order to generate higher yields of monoaryl substituted furanones, such as **8a**. Encouragingly, we found that by reducing the number of equivalents of 4-(trifluoromethyl)phenylboronic acid **6e** to 1.0, (*Z*)-4-bromo-5-(arylidene)furan-2(5*H*)-one **8c** could be isolated after flash column chromatography in 73% yield as an off-white solid (Scheme 1). The ^{1}H NMR spectrum of product **8c** was consistent with the formation of a monosubstituted product.



Scheme 1. Reaction and conditions: **6e** (1.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), CsF (3 equiv), Bu_4NI (0.05 equiv), toluene–H_2O (1:1), reflux, argon, 36 h.

To unambiguously determine the regioselectivity of the reaction, product **8c** was recrystallized from a mixture of dichloromethane and hexane. The X-ray crystal structure demonstrated the formation of the 5-monosubstituted furanone and was consistent with the results of the 2D HMBC NMR experiment (Fig. 4).

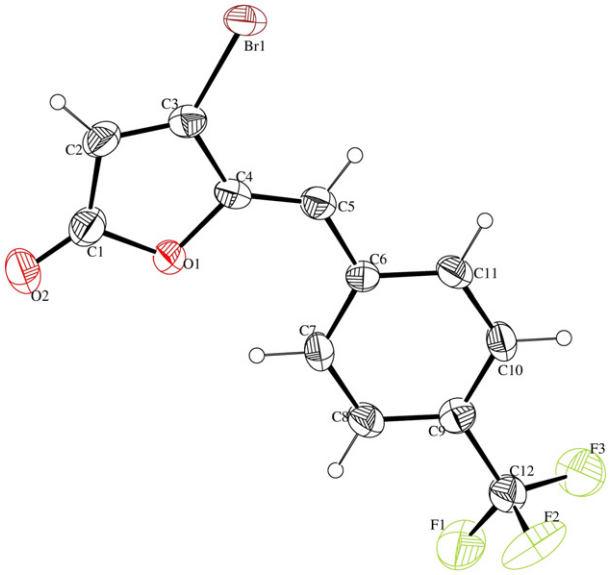


Fig. 4. Crystal structure of 5-aryl substituted furanone **8c**.[21]

Interestingly, further analysis of the X-ray crystal structure revealed the presence of oxygen–bromine halogen bonding. This intermolecular attraction was observed between the C4 bromine atom and the oxygen atom of the carbonyl group (Fig. 5). The geometrical parameters of the contacts included an interatomic distance (Br···O) of 3.12 Å and a bond angle (C–Br···O) of 169.3°. The Br···O distance was smaller than the sum of the van der Waals radii (3.37 Å) for Br···O, suggesting the presence of halogen bonding. The halogen-bonding is typically observed between a polarised halogen atom (a Lewis acid) and negatively-charged oxygen, nitrogen or sulfur atom (a Lewis base).[24,25] Oxygen-derived Lewis bases include the carbonyl, hydroxyl, charged carboxylate and phosphate groups. Halogen bonding has been reported to exist in many biological molecules, such as protein and nucleic acid structures, and has also been demonstrated to play significant roles in intermolecular recognition and self-assembly processes.[26]

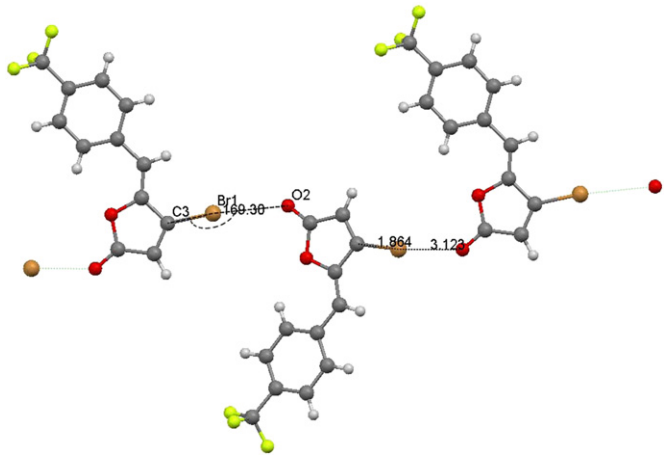
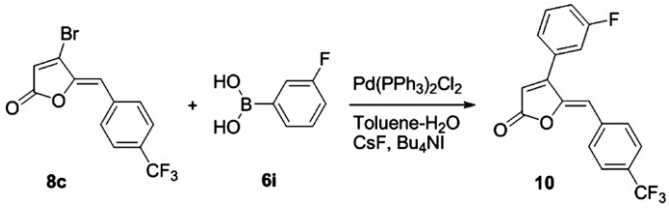


Fig. 5. Crystal structure of **8c** showing C–Br···O halogen bonding.[23]

Fimbrolides are generally difficult to crystallize, and the successful formation of the crystal structure for **8c** could be explained, at least in part, by the unexpected halogen bonding interactions.

After the successful preparation of 5-monosubstituted furanone **8c**, a second Suzuki reaction was attempted in order to generate an unsymmetrically substituted furanone product. Gratifyingly, treatment of **8c** with 3-fluorophenylboronic acid **6i** afforded 4-(3-fluorophenyl)-5-(4-(trifluoromethyl)benzylidene) furan-2(5*H*)-one **10** as a white solid in 69% yield (Scheme 2). This result demonstrates that the synthetic route described herein represents an efficient method for the synthesis of asymmetrically diaryl substituted furanones.



Scheme 2. Reaction and conditions: **6i** (1.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), CsF (3 equiv), Bu_4NI (0.05 equiv), toluene–H_2O (1:1), reflux, argon, 36 h.

3. Conclusions

We have successfully prepared a series of new 5-arylidenefuran-2(5*H*)-ones **7** and symmetrically substituted 5-arylidene-4-arylfuran-2(5*H*)-ones **9** via the Suzuki–Miyaura reactions of fimbrolide derivatives 5-(bromomethylene)furan-2(5*H*)-one **2** and 4-bromo-5-(bromomethylene)furan-2(5*H*)-one **3**, respectively. A regioselective Suzuki–Miyaura reaction on fimbrolide **3** furnished singly substituted 5-arylidene-4-bromofuran-2(5*H*)-ones **8a** and **8c**, which could undergo a second Suzuki–Miyaura reaction to furnish the asymmetrically substituted 5-arylidene-4-arylfuran-2(5*H*)-one **10**. The X-ray crystal structure of intermediate **8c** revealed interesting Br···O halogen bonding behaviour that could account for the ease of crystallization of this compound compared to other fimbrolide derivatives.

4. Experimental

4.1. General methods

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Elemental analyses were performed by the Campbell Microanalytical Laboratory, University of Otago, New Zealand. Infrared spectra were obtained on a Mattson Genesis series FTIR spectrometer. Ultraviolet spectra were measured on Carey 100 spectrophotometers. ^{1}H NMR spectra were recorded at 300 MHz with a Bruker AC300F and NMR spectral data are reported as follows: chemical shift measured in parts per million (ppm) downfield from TMS (δ); multiplicity; observed coupling constant (J) in Hertz (Hz); proton count; assignment. Multiplicities are recorded as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), quintet (p), multiplet (m), doublet of doublets (dd), doublet of triplets (dt) and combinations of these. ^{13}C NMR chemical shifts are reported in ppm downfield from TMS (δ), and identifiable carbons are given. The EI mass spectra were measured using a VG Quattro mass spectrometer at 70 eV ionization voltage and 200 °C ion source temperature. The principle ion peaks m/z are reported together with their percentage intensities relative to the base peak. Column chromatography was performed using Merck 60 Silica Gel whilst preparative thin layer chromatography was performed on 20×20×0.1 cm plates using Merck silica gel 7730 $60GF_{254}$. Compounds were detected by short and long wavelength ultraviolet light.

4.1.1. 5-(4-Fluorobenzylidene)furan-2(5H)-one ***7a***. A mixture of furanone **2** (0.15 g, 0.86 mmol), 4-fluorophenylboronic acid **6a** (0.14 g, 1.03 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.030 g, 0.043 mmol), tetrabutylammonium iodide (0.016 g, 0.043 mmol) and caesium fluoride (0.39 g, 2.58 mmol) in toluene–water (1:1, 20 mL) was heated to reflux under argon for 36 h. Brine (40 mL) was added and the mixture was extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure to give the crude product. The crude product was purified using flash column chromatography with dichloromethane/light petroleum (1/1) to afford the desired furanone as a white solid (0.122 g, 75%). Mp 140–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.76 (m, 2H, ArH), 7.49 (d, 1H, J=5.3 Hz, H4), 7.11–7.05 (m, 2H, ArH), 6.21 (d, 1H, J=5.3 Hz, H3), 5.99 (s, 1H,]CH). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 170.0, 161.3, 147.9, 145.1, 132.6 (d), 129.0, 118.0, 115.9 (d), 112.9. UV (CH_3OH) λ_{max} 201 nm (ε 19,226 $M^{-1}cm^{-1}$), 225 (20,158), 331 (54,959). IR (KBr) υ_{max}1740, 1601, 1548, 1506, 1368, 1234, 1185, 1166, 1114, 1094, 1071, 931, 887, 853, 835, 821, 781, 765 cm^{-1}. HRMS (ESI) m/z found 191.0505; $C_{11}H_8FO_2$ $(M+H)^+$ requires 191.0508 (100%).

4.1.2. 5-(4-Methoxybenzylidene)furan-2(5H)-one ***7b***. This compound was prepared by the same method as compound **7a**, from furanone **2** (0.15 g, 0.86 mmol), 4-methoxyphenylboronic acid **6b** (0.16 g, 1.03 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.030 g, 0.043 mmol), tetrabutylammonium iodide (0.016 g, 0.043 mmol), caesium fluoride (0.39 g, 2.58 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a white solid (0.139 g, 80%). Mp 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J=5.9 Hz, 2H, ArH), 7.46 (d, J=5.3 Hz, 1H, H4), 6.92 (d, J=6.9 Hz, 2H, ArH), 6.15 (d, J=5.3 Hz, 1H, H3), 5.99 (s, 1H,]CH), 3,84 (s, 3H, OCH_3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 170.5, 160.5, 147.0, 145.1, 132.4, 125.6, 116.8, 114.3, 114.2, 55.3. UV (CH_3OH) λ_{max} 202 nm (ε 10,550 $M^{-1}cm^{-1}$), 239 (8647), 359 (22,052). IR (KBr) υ_{max}1748, 1604, 1551, 1446, 1366, 1302, 1257, 1119, 1025, 930, 893, 882, 813, 770, 680 cm^{-1}. HRMS (ESI) m/z found 203.0701; $C_{12}H_{11}O_3$ $(M+H)^+$ requires 203.0708 (100%).

4.1.3. 5-(Thiophen-2-ylmethylene)furan-2(5H)-one ***7c***. This compound was prepared by the same method as compound **7a**, from furanone **2** (0.15 g, 0.86 mmol), thiophen-2-ylboronic acid **6c** (0.13 g, 1.03 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.030 g, 0.043 mmol), tetrabutylammonium iodide (0.016 g, 0.043 mmol), caesium fluoride (0.39 g, 2.58 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as

a white solid (0.095 g, 62%). Mp 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, J=0.8, 3.5 Hz, 1H, ArH), 7.45 (d, J=5.3 Hz, 1H, H4), 7.38 (dd, J=0.7, 5.1 Hz, 1H, ArH), 7.08–7.05 (m, 1H, ArH), 6.30 (s, 1H,]CH), 6.17 (d, J=5.3 Hz, 1H, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 169.5, 146.6, 143.7, 135.9, 131.3, 130.8, 127.7, 118.0, 107.5. UV (CH_3OH) λ_{max} 203 nm (ε 11,782 $M^{-1}cm^{-1}$), 234 (8396), 362 (22,138). IR (KBr) υ_{max}1737, 1645, 1544, 1415, 1370, 1335, 1244, 1108, 1070, 936, 886, 795, 733, 688 cm^{-1}. HRMS (ESI) m/z found 179.0157; $C_9H_7O_2S$ $(M+H)^+$ requires 179.0167 (100%).

4.1.4. 5-(Thiophen-3-ylmethylene)furan-2(5H)-one ***7d***. This compound was prepared by the same method as compound **7a**, from furanone **2** (0.15 g, 0.86 mmol), thiophen-3-ylboronic acid **6d** (0.13 g, 1.03 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.030 g, 0.043 mmol), tetrabutylammonium iodide (0.016 g, 0.043 mmol), caesium fluoride (0.39 g, 2.58 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a white solid (0.105 g, 69%). Mp 61–63 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.73 (m, 1H, ArH), 7.51 (dd, J=1.2, 5.1 Hz, 1H, ArH), 7.45 (d, J=5.3 Hz, 1H, H4), 7.32 (dd, J=2.9, 5.1 Hz, 1H, ArH), 6.17 (d, J=5.3 Hz, 1H, H3), 6.10 (s, 1H,]CH). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 170.0, 147.4, 144.6, 134.2, 128.8, 128.6, 126.2, 117.9, 108.9. UV (CH_3OH) λ_{max} 204 nm (ε 17,286 $M^{-1}cm^{-1}$), 237 (8279), 337 (29,097). IR (KBr) υ_{max}1747, 1604, 1550, 1509, 1446, 1366, 1257, 1175, 1110, 1075, 1025, 931, 892, 812, 769, 680 cm^{-1}. HRMS (ESI) m/z found 179.0160; $C_9H_7O_2S$ $(M+H)^+$ requires 179.0167 (100%).

4.1.5. 5-(4-(Trifluoromethyl)benzylidene)furan-2(5H)-one ***7e***. This compound was prepared by the same method as compound **7a**, from furanone **2** (0.15 g, 0.86 mmol), 4-(trifluoromethyl)phenylboronic acid **6e** (0.20 g, 1.03 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.030 g, 0.043 mmol), tetrabutylammonium iodide (0.016 g, 0.043 mmol), caesium fluoride (0.39 g, 2.58 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a white solid (0.159 g, 77%). Mp 59–61 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J=8.2 Hz, 2H, ArH), 7.62 (d, J=8.2 Hz, 1H, ArH), 7.50 (d, J=5.4 Hz, 2H, H4), 6.27 (d, J=5.4 Hz, 1H, H3), 6.03 (s, 1H,]CH). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 169.5, 149.6, 145.0, 136.0, 130.7, 130.2 (t), 125.6, 122.0, 119.3, 112.1. UV (CH_3OH) λ_{max} 201 nm (ε 11,809 $M^{-1}cm^{-1}$), 223 (10,988), 326 (27,401). IR (KBr) υ_{max}1749, 1653, 1605, 1549, 1508, 1344, 1285, 1224, 1166, 1071, 934, 884, 894, 821 cm^{-1}. HRMS (ESI) m/z found 241.0465; $C_{12}H_7F_3O_2$ $(M+H)^+$ requires 241.0476 (100%).

4.1.6. 5-(3-(Trifluoromethyl)benzylidene)furan-2(5H)-one ***7f***. This compound was prepared by the same method as compound **7a**, from furanone **2** (0.15 g, 0.86 mmol), 3-(trifluoromethyl)phenylboronic acid **6f** (0.20 g, 1.03 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.030 g, 0.043 mmol), tetrabutylammonium iodide (0.016 g, 0.043 mmol), caesium fluoride (0.39 g, 2.58 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a white solid (0.154 g, 75%). Mp 65–67 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J=6.8 Hz, 1H, ArH), 7.90 (s, 1H, ArH), 7.53–7.50 (m, 2H, ArH), 7.48 (d, J=5.3 Hz, 1H, H4), 6.25 (d, J=5.3 Hz, 1H, H3), 6.01 (s, 1H,]CH). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 169.5, 149.3, 145.0, 133.4, 131.4, 130.9, 129.3, 127.0, 125.5 (t), 121.9, 119.1, 112.1. UV (CH_3OH) λ_{max} 202 nm (ε 18,374 $M^{-1}cm^{-1}$), 223 (14,811), 322 (41,871). IR (KBr) υ_{max}1758, 1650, 1551, 1326, 1300, 1221, 1189, 1164, 1134, 1108, 1097, 1079, 942, 899, 860, 812, 798, 690 cm^{-1}. HRMS (ESI) m/z found 239.0326; $C_{12}H_6F_3O_2$ $(M-H^+)^-$ requires 239.0325 (100%).

4.1.7. 5-(4-Nitrobenzylidene)furan-2(5H)-one ***7g***. This compound was prepared by the same method as compound **7a**, from furanone **2** (0.15 g, 0.86 mmol), 4-nitrophenylboronic acid **6g** (0.17 g, 1.03 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.030 g, 0.043 mmol), tetrabutylammonium iodide (0.016 g, 0.043 mmol), caesium fluoride (0.39 g, 2.58 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a yellow solid (0.158 g, 85%). Mp 189–192 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J=9.2 Hz, 2H, ArH), 7.93 (d, J=8.9 Hz, 1H, ArH), 7.55 (d, J=5.4 Hz, 2H, H4), 6.35 (d, J=5.4 Hz, 1H, H3), 6.08 (s, 1H,]CH). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 169.0, 150.5, 147.2, 144.9, 138.9, 131.0, 123.9, 120.1, 111.0. UV (CH_3OH) λ_{max} 201 nm (ε 11,809 $M^{-1}cm^{-1}$), 223 (10,988), 326 (27,401). IR (KBr) υ_{max}1793, 1560, 1554, 1513, 1344, 1102, 1063, 935, 876, 823, 804, 749, 690 cm^{-1}. HRMS (ESI) m/z found 216.0318; $C_{11}H_6NO_4$ $(M-H^+)^-$ requires 216.0302 (100%).

4.1.8. 5-(4-(Trifluoromethoxy)benzylidene)furan-2(5H)-one ***7h***. This compound was prepared by the same method as compound **7a**, from furanone **2** (0.15 g, 0.86 mmol), 4-(trifluoromethoxy)phenylboronic acid **6h** (0.21 g, 1.03 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.030 g, 0.043 mmol), tetrabutylammonium iodide (0.016 g, 0.043 mmol), caesium fluoride (0.39 g, 2.58 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a yellow solid (0.145 g, 66%). Mp 62–64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J=8.8 Hz, 2H, ArH), 7.48 (d, J=5.5 Hz, 1H, H4), 7.20 (d, J=8.8 Hz, 2H, ArH), 6.22 (d, J=5.5 Hz, 1H, H3), 5.99 (s, 1H,]CH). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 169.7, 149.4, 148.6, 145.0, 132.0, 131.3, 121.8, 120.9, 118.5, 112.3. UV (CH_3OH) λ_{max} 201 nm (ε 14,141 $M^{-1}cm^{-1}$), 224 (13,629), 326 (34,021). IR (KBr) υ_{max}1749, 1605, 1549, 1509, 1277, 1222, 1166, 1117, 1071, 934, 885, 822, 769 cm^{-1}. HRMS (ESI) m/z found 255.0276; $C_{12}H_6F_3O_3$ $(M-H^+)^-$ requires 255.0275 (100%).

4.1.9. 4-Bromo-5-(2,4-difluorobenzylidene)furan-2(5H)-one ***8a*** *and 5-(2,4-difluorobenzylidene)-4-(2,4-difluorophenyl)furan-2(5H)-one* ***9c***. A mixture of furanone **3** (0.20 g, 0.79 mmol), 2,4-difluorophenylboronic acid **6j** (0.25 g, 1.58 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.055 g, 0.079 mmol), tetrabutylammonium iodide (0.030 g, 0.079 mmol) and caesium fluoride (0.72 g, 4.74 mmol) in toluene–water (1:1, 20 mL) was heated to reflux under argon for 36 h. Brine (40 mL) was added and the mixture was extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure to give the crude product. The crude product was purified using gravity column chromatography with dichloromethane/light petroleum (1/2) to afford the furanone **8a** as a white solid (0.054 g, 24%) and the furanone **9c** as white solid (0.068 g, 27%).

4.1.10. 4-Bromo-5-(2,4-difluorobenzylidene)furan-2(5H)-one ***8a***. Mp 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19–8.11 (m, 1H, ArH), 6.93–6.87 (m, 1H, ArH), 6.81–6.77 (m, 1H, ArH), 6.52 (s, 1H,]CH), 6.38 (s, 1H, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 165.8, 150.1 (d), 146.2, 137.6, 134.8, 133.1 (d), 121.4, 119.7, 112.7 (d), 103.9, 102.4. UV (CH_3OH) λ_{max} 200 nm (ε 59,821 $M^{-1}cm^{-1}$), 252 (18,003). IR (KBr) υ_{max} 1779, 1613, 1558, 1550, 1550, 1434, 1273, 1146, 1107, 1088, 967, 910, 833, 800, 611, 580 cm^{-1}. HRMS (ESI) m/z found 308.9344; $C_{11}H_5BrF_2NaO_2$ $(M+Na)^+$ requires 308.9339 (100%).

4.1.11. 5-(2,4-Difluorobenzylidene)-4-(2,4-difluorophenyl)furan-2(5H)-one ***9c***. Mp 144–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.28 (m, 2H, ArH), 7.03–6.88 (m, 4H, ArH), 6.18 (s, 1H,]CH), 6.06 (s, 1H, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 168.5, 163.1, 162.5, 159.8 (d), 158.7 (d), 151.1, 148.6, 133.8 (d), 132.0 (d), 118.0, 112.9 (d), 112.6 (d), 105.8, 105.5, 104.6, 104.3, 103.9. UV (CH_3CN) λ_{max} 231 nm (ε 2796 $M^{-1}cm^{-1}$), 297 (5592). IR (KBr) υ_{max} 3105, 1775, 1621, 1481, 1455, 1346, 1235, 1208, 1116, 1100, 964, 927, 873, 750 cm^{-1}. HRMS

(ESI) *m*/*z* found 321.0534; $C_{17}H_9F_4O_2$ $(M+H)^+$ requires 321.0539 (100%).

4.1.12. 4-Bromo-5-(4-(trifluoromethyl)benzylidene)furan-2(5H)-one ***8c***. This compound was prepared by the same method as compound **7a**, from furanone **3** (0.20 g, 0.79 mmol), 4-(trifluoromethyl)phenylboronic acid **6e** (0.15 g, 0.79 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.028 g, 0.040 mmol), tetrabutylammonium iodide (0.015 g, 0.040 mmol), caesium fluoride (0.35 g, 2.37 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a white solid (0.096 g, 73%). Mp 114–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J*=8.5 Hz, 2H, ArH), 7.64 (d, *J*=8.3 Hz, 2H, ArH), 6.46 (s, 1H,]CH), 6.35 (s, 1H, H3). ^{13}C NMR (75.6 MHz, CDCl3) δ 166.5, 147.9, 138.4, 135.2, 131.4, 130.8, 125.7 (t), 121.8, 119.8, 111.3. UV (CH_3OH) λ_{max} 202 nm (ε 8195 $M^{-1}cm^{-1}$), 224 (6517), 326 (11,327). IR (KBr) υ_{max} 1766, 1554, 1325, 1217, 1163, 1113, 1070, 1018, 972, 912, 872, 804 cm^{-1}. HRMS (ESI) *m*/*z* found 316.9435; $C_{12}H_6BrF_3O_2$ $(M-H^+)^-$ requires 316.9431(100%).

4.1.13. 5-(4-Fluorobenzylidene)-4-(4-fluorophenyl)furan-2(5H)-one ***9a***. This compound was prepared by the same method as compound **7a**, from furanone **3** (0.20 g, 0.79 mmol), 4-fluorophenylboronic acid **6a** (0.28 g, 1.98 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.055 g, 0.079 mmol), tetrabutylammonium iodide (0.030 g, 0.079 mmol), caesium fluoride (0.72 g, 4.74 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a white solid (0.155 g, 69%). Mp 188–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.71 (m, 2H, ArH), 7.45–7.41 (m, 2H, ArH), 7.16–7.13 (m, 2H, ArH), 7.05–6.99 (m, 2H, ArH), 6.13 (s, 1H,]CH), 6.02 (s, 1H, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 168.9, 166.1, 162.8 (d), 158.0 (d), 148.0, 133.1 (d), 130.8 (d), 129.5, 126.8 (d), 116.7 (d), 116.4, 114.9, 112.9. UV (CH_3OH) λ_{max} 226 nm (ε 32,514 $M^{-1}cm^{-1}$), 275 (25,522). IR (KBr) υ_{max} 1746, 1606, 1503, 1231, 1159, 1083, 954, 926, 825, 585 cm^{-1}. HRMS (ESI) *m*/*z* found 307.0547; $C_{17}H_{10}F_2NaO_2$ $(M+Na)^+$ requires 307.0548 (100%).

4.1.14. 5-(3-Fluorobenzylidene)-4-(3-fluorophenyl)furan-2(5H)-one ***9b***. This compound was prepared by the same method as compound **7a**, from furanone **3** (0.20 g, 0.79 mmol), 3-fluorophenylboronic acid **6i** (0.28 g, 1.98 mmol), dichlorobis (triphenylphosphine) palladium(II) (0.055 g, 0.079 mmol), tetrabutylammonium iodide (0.030 g, 0.079 mmol), caesium fluoride (0.72 g, 4.74 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a white solid (0.197 g, 88%). Mp 113–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.78 (m, 2H, ArH), 7.52–7.48 (m, 2H, ArH), 7.26–7.20 (m, 2H, ArH), 7.12–7.06 (m, 2H, ArH), 6.20 (s, 1H,]CH), 6.09 (s, 1H, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 168.3, 166.4, 163.0 (d), 157.3 (d), 145.2, 133.7 (d), 130.9, 130.5, 128.8 (d), 117.9 (d), 115.4 (d), 114.3, 108.1. UV (CH_3OH) λ_{max} 270 nm (ε 16,280 $M^{-1}cm^{-1}$), 368 (444). IR (KBr) υ_{max} 3098, 1770, 1575, 1490, 1431, 1272, 1242, 1196, 1180, 1165, 928, 874, 857, 779 cm^{-1}. HRMS (ESI) *m*/*z* found 307.0547; $C_{17}H_{10}F_2NaO_2$ $(M+Na)^+$ requires 307.0541 (100%).

4.1.15. 5-(2-Fluorobenzylidene)-4-(2-fluorophenyl)furan-2(5H)-one ***9d***. This compound was prepared by the same method as compound **7a**, from furanone **3** (0.20 g, 0.79 mmol), 2-fluorophenylboronic acid **6l** (0.28 g, 1.98 mmol), dichlorobis (triphenylphosphine) palladium(II) (0.055 g, 0.079 mmol), tetrabutylammonium iodide (0.030 g, 0.079 mmol), caesium fluoride (0.72 g, 4.74 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a white solid (0.213 g, 95%). Mp 158–161 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35–8.30 (m, 1H, ArH), 7.58–7.46 (m, 3H, ArH), 7.38–7.21 (m, 3H, ArH), 7.11–7.04 (m, 1H, ArH), 6.39 (s, 1H,]CH), 6.38 (s, 1H, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 168.9, 162.9(d), 159.5 (d), 152.5, 148.9, 132.7 (d), 132.1, 131.4 (d), 130.9, 125.1(d), 121.5, 118.2, 118.0, 116.9, 115.8 (d), 115.5104.9. UV (CH_3OH) λ_{max} 226 nm (ε 27,980 $M^{-1}cm^{-1}$). IR (KBr) υ_{max} 3105, 1775, 1621, 1481, 1455, 1346, 1235, 1208, 1116, 1100, 964, 927, 873, 750 cm^{-1}. HRMS (ESI) *m*/*z* found 307.0547; $C_{17}H_{10}F_2NaO_2$ $(M+Na)^+$ requires 307.0553 (100%).

4.1.16. 5-(4-Methylbenzylidene)-4-p-tolylfuran-2(5H)-one ***9e***. This compound was prepared by the same method as compound **7a**, from furanone **3** (0.20 g, 0.79 mmol), *p*-tolylboronic acid **6m** (0.27 g, 1.98 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.055 g, 0.079 mmol), tetrabutylammonium iodide (0.030 g, 0.079 mmol), caesium fluoride (0.72 g, 4.74 mmol) and toluene–-water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a brown oil (0.200 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J*=8.3 Hz, 2H, ArH), 7.33 (d, *J*=8.1 Hz, 2H, ArH), 7.25 (d, *J*=8.1 Hz, 2H, ArH), 7.12 (d, *J*=8.1 Hz, 2H, ArH), 6.10 (s, 1H,]CH), 6.08 (s, 1H, H3), 2.37 (s, 3H, CH_3), 2.30 (s, 3H, CH_3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 169.6, 159.2, 147.9, 141.2, 140.1, 131.2, 130.7, 130.2, 130.0, 128.9, 128.1, 114.4, 114.0, 21.90, 21.84. UV (CH_3OH) λ_{max} 238 nm (ε 15,641 $M^{-1}cm^{-1}$), 346 (23,811). IR (KBr) υ_{max} 1751, 1643, 1572, 1332, 1240, 1180, 1083, 921, 850, 790, 691 cm^{-1}. HRMS (ESI) *m*/*z* found 299.1053; $C_{19}H_{16}NaO_2$ $(M+Na)^+$ requires 299.1048 (100%).

4.1.17. 5-(3-Methylbenzylidene)-4-m-tolylfuran-2(5H)-one ***9f***. This compound was prepared by the same method as compound **7a**, from furanone **3** (0.20 g, 0.79 mmol), *m*-tolylboronic acid **6n** (0.27 g, 1.98 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.055 g, 0.079 mmol), tetrabutylammonium iodide (0.030 g, 0.079 mmol), caesium fluoride (0.72 g, 4.74 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a brown oil (0.139 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H, ArH), 7.37–7.19 (m, 6H, ArH), 7.10 (s, 1H, ArH), 6.12 (s, 1H, H3), 6.09 (s, 1H,]CH), 2.38 (s, 3H, CH_3), 2.31 (s, 3H, CH_3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 169.5, 159.5, 148.3, 139.4, 138.8, 133.3, 131.7, 131.6, 130.8, 130.6, 129.5, 129.3, 129.1, 128.5, 126.0, 114.7, 114.5, 21.84, 21.81. UV (CH_3OH) λ_{max} 238 nm (ε 10,664 $M^{-1}cm^{-1}$), 339 (17,257). IR (KBr) υ_{max} 1752, 1643, 1572, 1349, 1240, 1180, 1083, 922, 851, 790, 707, 691 cm^{-1}. HRMS (ESI) *m*/*z* found 299.1053; $C_{19}H_{16}NaO_2$ $(M+Na)^+$ requires 299.1048 (100%).

4.1.18. 5-(4-Cyanobenzylidene)-4-(4-cyanophenyl)furan-2(5H)-one ***9g***. This compound was prepared by the same method as compound **7a**, from furanone **3** (0.20 g, 0.79 mmol), 4-cyanophenylboronic acid **6o** (0.29 g, 1.98 mmol), dichlorobis (triphenylphosphine) palladium(II) (0.055 g, 0.079 mmol), tetrabutylammonium iodide (0.030 g, 0.079 mmol) caesium fluoride (0.72 g, 4.74 mmol) and toluene–water (1:1, 20 mL). After chromatography, the desired furanone was obtained as a brown solid (0.089 g 38%). Mp 132–134 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J*=8.5 Hz, 2H, ArH), 7.64 (d, *J*=8.7 Hz, 2H, ArH), 7.38 (d, *J*=8.7 Hz, 2H, ArH), 7.35 (d, *J*=8.6 Hz, 2H, ArH), 6.13(s, 1H,]CH), 6.10 (s, 1H, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 169.9, 159.6, 147.8, 142.5, 141.1, 131.0, 130.9, 130.4, 132.0, 128.7, 128.3, 118.7, 118.3, 114.8, 112.0. UV (CH_3OH) λ_{max} 234 nm (ε 16,320 $M^{-1}cm^{-1}$), 319 (25,360). IR (KBr) υ_{max} 3801, 2901, 1748, 1655, 1523, 1342, 1098, 1045, 937, 829, 731, 688 cm^{-1}. HRMS (ESI) *m*/*z* found 321.0633; $C_{19}H_{10}N_2NaO_2$ $(M+Na)^+$ requires 321.0640 (100%).

4.1.19. 4-(3-Fluorophenyl)-5-(4-(trifluoromethyl)benzylidene) furan-2(5H)-one ***10***. This compound was prepared by the same method as compound **7a**, from furanone **8c** (0.10 g, 0.31 mmol), 3-fluorophenylboronic acid **6i** (0.052 g, 0.37 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.021 g, 0.015 mmol), tetrabutylammonium iodide (0.006 g, 0.015 mmol), caesium fluoride (0.14 g, 2.37 mmol) and toluene–water (1:1, 20 mL).The desired furanone was obtained as a yellow solid (0.054 g, 52%). Mp

58–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J=8.2 Hz, 2H, ArH), 7.62 (d, J=8.4 Hz, 2H, ArH), 7.55–7.47 (m, 1H, ArH), 7.30–7.18 (m, 3H, ArH), 6.27 (s, 1H,]CH), 6.15 (s, 1H, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 167.7, 164.4, 161.1, 157.1 (d), 148.9, 136.0, 131.8 (d), 130.7 (d), 128.8, 125.6 (m), 124.2 (d), 121.9, 117.7, 116.0, 115.7, 111.7. UV (CH_3OH) λ_{max} 202 nm (ε 17,525 $M^{-1}cm^{-1}$), 240 (7688), 334 (13,394). IR (KBr) υ_{max} 1766, 1576, 1485, 1332, 1270, 1170, 1161, 1106, 1070, 1016, 932, 865, 843, 794, 692 cm^{-1}. HRMS (ESI) m/z found 333.0545; $C_{18}H_{10}F_4O_2$ $(M-H^+)^-$ requires 333.0544(100%).

Acknowledgements

We thank the University of New South Wales and the Australian Research Council's Discovery Projects funding scheme (project number DP1095159).

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.02.014.

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