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A convenient access to furo[3,2-*c*]pyridin-6(5*H*)-ones by the reaction of 5-iodo-4-methoxy-2-pyridones with terminal alkynes under microwave-enhanced Sonogashira conditions

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ABSTRACT

N-Alkyl-3-aryl-5-iodo-4-methoxypyridin-2(1*H*)-ones readily undergo sequential acetylide cross-coupling, demethylation, and furan annulation under classical Sonogashira reaction conditions to furnish 7-arylfuro[3,2-*c*]pyridin-4(5*H*)-ones, a class of hitherto unknown compounds, in a one-pot operation. Microwave irradiation was found to significantly reduce reaction times and to allow lower catalysts and reagent loadings.

The phenyl(dihydro)furopyridinone system is present in several structurally and biologically interesting fungal metabolites, which have been recently reported as antibacterial or antifungal antibiotics.[1] Two differently fused ring systems are found in these natural products, namely the phenylfuro[2,3-*b*]pyridin-4-one **I** and the regioisomeric phenylfuro[3,2-*c*]pyridin-4-one **II** systems. Synthetic efforts toward this class of compounds have already been reported in the literature.[2] In the present work, we examined the possibility of synthesizing arylfuropyridones of type **III** prompted by the fact that, to the best of our knowledge, the furo[3,2-*c*]pyridin-6-one ring system has never been reported in the literature (Fig. 1).

Recently, we have shown that 5-aryl-3-iodopyridin-2-ones **1** can give easy access to 2-substituted furan derivatives **2** through in situ sequential Sonogashira-acetylide coupling, demethylation, and furan annulation reactions. In this one-pot process, Et_3N-promoted S_N2 demethylation of the intermediate 3-alkynyl-4-methoxypyridin-2-ones was found to induce metal-free anionic heteroannulation (Scheme 1, Eq. 1).[3] We envisioned this methodology to be applicable to the synthesis of the regioisomeric arylfuropyridones **4** (Scheme 1, Eq. 2).

First, we prepared a series of 3-aryl-5-iodo-4-methoxy-2-pyridones **3a–e**, which proved to be easily accessible in high yields from readily available 3-iodo-2-pyridones **5**[4] through Suzuki–Miyaura cross-coupling reactions[5], followed by C-5 iodination of

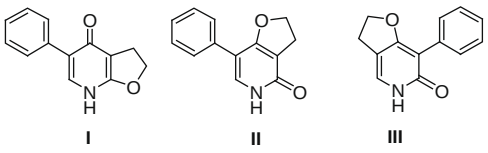
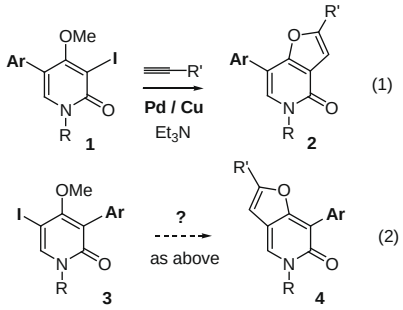


Figure 1. Regioisomeric phenylfuropyridinone ring systems.



Scheme 1.

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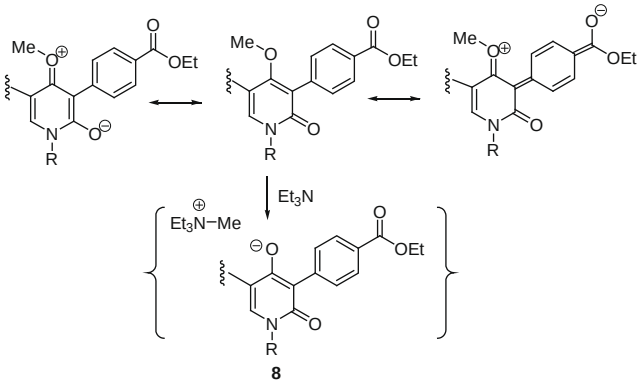
the resulting arylpyridone by *N*-iodosuccinimide in the presence of TFA[6] (Table 1).

The first assays to determine the viability of 5-iodo-2-pyridones participating in the coupling–demethylation–annulation process were carried out by using our previously reported reaction conditions. A series of model substrates including electron-rich and electron-poor arylpyridones (**3a, b, e**) were selected to evaluate possible electronic effects on the rate of reactions. The latter were heated at 80 °C in Et_3N/DMF (2:1) in the presence of 3 equiv of a terminal alkyne, 10 mol % $PdCl_2(PPh_3)_2$, and 20 mol % CuI for 5 days. The results are summarized in Table 2. As can be seen, the desired compounds **4** were obtained in isolated yields ranging from 20% to 78% depending essentially on the nature of the pyridone-substituted arene.[7] As illustrated with the reactions of **3a** (Table 2, entries 1–3), the presence of an electron-donating group on the arylpyridone had a negative effect on the rate of the dealkylation process, which left substantial amounts of alkynylpyridone intermediates **7** unreacted. Conversely, best results were obtained with an electron-poor arylic group (Table 2, entries 5–7). Indeed, it is expected that the presence of an electron-withdrawing group, such as an ester group, on the arylic moiety of the starting pyridone would favor cleavage of the methyl ether by triethylamine, as this generates a highly stabilized triethylmethyl ammonium enolate **8** (Scheme 2). On the other hand, the nature of the arylacetylene partner did not exert significant influence on the rate of the reaction.

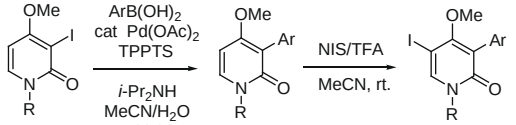
Despite this success, we were concerned that the present process had two considerable drawbacks: (1) reaction times are very long which render the production of the desired furopyridones by this method particularly inconvenient, and (2) high catalyst loadings as well as large excesses of the alkyne partner are required. We therefore envisaged the possibility of accelerating this process by using microwave catalysis. After some experimentation, we established a successful microwave protocol[8] using MeCN as solvent that allowed low catalysts and alkyne loading coupling reactions as well as rapid and complete furan formation. The results are summarized in Table 3. As in the conventional protocol, it was found that pyridones bearing an electron-rich arylic group reacted more slowly, but still gave good yields of the desired furopyridones within reasonable reaction times under microwave irradiation (compare entries 1–3 in Tables 2 and 3). As illustrated with the reaction of 1-hexyne (Table 3, entries 6), alkyl-substituted acetylenes participated less efficiently in the process.

In summary, we have shown that microwave-assisted reaction of 3-aryl-5-iodo-4-methoxy-2-pyridones with terminal alkynes under Sonogashira conditions provides an easy and efficient access to hitherto unknown arylfuro[3,2-*c*]pyridin-6-one derivatives[9] through sequential acetylide cross-coupling, *O*-dealkylation, and anionic annulation reactions. Further investigation into the scope and limitations of this process is underway.



Scheme 2.

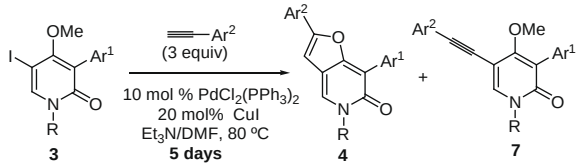
Table 1
Synthesis of 3-aryl-5-iodo-2-pyridones **3a–e**[a]



Entry	Pyridone **5** R=	Boronic acid Ar=	**6**; yield (%)	**3**; yield (%)
1	Me	*p*-MeOPh	**6a**; 89	**3a**; 95
2	Me	Ph	**6b**; 82	**3b**; 74
3	Me	*p*-CO_2EtPh	**6c**; 90	**3c**; 52
4	Me	*m*-CF_3Ph	**6d**; 87	**3d**; 92
5	Bn	*p*-CO_2EtPh	**6e**; 88	**3e**; 98

[a] TPPTS: tris(3-sulfonatophenyl)phosphane trisodium salt.

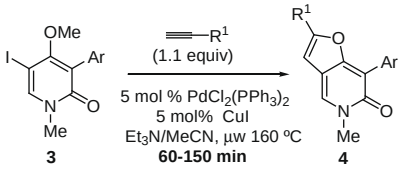
Table 2
Synthesis of arylfuropyridones **4a–g** under conventional heating[a]



Entry	Starting iodopyridone		Alkyne Ar^2=	Products yield (%) **4** (**7**)
	R=	Ar^1=		
1	**3a** Me	*p*-MeOPh	Ph	**4a**; 20 (**7a**; 74)
2	**3a** Me	*p*-MeOPh	*p*-MeOPh	**4b**; 27 (**7b**; 70)
3	**3a** Me	*p*-MeOPh	*p*-CO_2MePh	**4c**; 33 (**7c**; 43)
4	**3b** Me	Ph	Ph	**4d**; 60 (**7d**; 38)
5	**3e** Bn	*p*-CO_2EtPh	Ph	**4e**; 78 (**7e**; 18)
6	**3e** Bn	*p*-CO_2EtPh	*p*-MeOPh	**4f**; 61 (**7f**; 28)
7	**3e** Bn	*p*-CO_2EtPh	*p*-CO_2MePh	**4g**; 77 (**7g**; 19)

[a] Isolated yields (single runs).

Table 3
Synthesis of arylfuropyridones **4a–c** and **4h–j** under micro-wave irradiation[a]



Entry	Starting iodopyridone Ar=		Alkyne R^1=	Time (min)	Product **4**; yield (%)
1	*p*-MeOPh	(**3a**)	Ph	150	**4a**; 80
2	*p*-MeOPh	(**3a**)	*p*-MeOPh	150	**4b**; 73
3	*p*-MeOPh	(**3a**)	*p*-CO_2MePh	150	**4c**; 93
4	*p*-CO_2EtPh	(**3c**)	*p*-MeOPh	60	**4h**; 78
5	*m*-CF_3Ph	(**3d**)	Ph	60	**4i**; 94
6	*m*-CF_3Ph	(**3d**)	*n*-Bu	120	**4j**; 66[b]

[a] Isolated yields (single runs).
[b] 3 equiv of 1-hexyne was used.

Acknowledgments

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5. *Representative experimental procedure*: A solution of the selected 3-iodo-2-pyridone (0.2 mmol), the boronic acid (0.3 mmol), $Pd(OAc)_2$ (0.01 mmol), TPPTS (21 mg, 0.03 mmol), and diisopropylamine (0.6 mmol) in a mixture of MeCN (3 mL) and water (1 mL) was left to stir at 80 °C for 16 h under Ar, and then concentrated in vacuo. The residue was purified by column chromatography (silica gel, acetone/CH_2Cl_2) to give the corresponding 3-aryl-2-pyridone. Selected data: Compound **6a**: Mp: 108–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.54 (s, NMe), 3.78 (s, OMe), 3.83 (s, OMe), 6.15 (d, J = 7.7 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 7.7 Hz, 1H), 7.43 (d, J = 8.8 Hz, 2H). Compound **6b**: Mp: 90–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.55 (s, NMe), 3.78 (s, OMe), 6.17 (d, J = 7.7 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.35–7.52 (m, 5H). Compound **6c**: Mp: 117–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, J = 7.3 Hz, 3H), 3.48 (s, NMe), 3.72 (s, OMe), 4.31 (q, J = 7.3 Hz, 2H), 6.11 (d, J = 7.7 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.99 (d, J = 8.3 Hz, 2H). Compound **6d**: Mp: 124–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.52 (s, NMe), 3.77 (s, OMe), 6.15 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.43–7.52 (m, 2H), 7.64 (d, J = 7.1 Hz, 1H), 7.72 (s, 1H). Compound **6e**: Mp: 130–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, J = 7.2 Hz, 3H), 3.76 (s, OMe), 4.36 (q, J = 7.2 Hz, 2H), 5.15 (s, 2H), 6.14 (d, J = 7.7 Hz, 1H), 7.30–7.35 (m, 5H), 7.39 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 8.09 (d, J = 8.5 Hz, 2H).
6. *Representative experimental procedure*: A solution of the selected 3-aryl-2-pyridone (0.7 mmol) and NIS (0.77 mmol) in 2 mL MeCN was treated with TFA (0.7 mmol), and the reaction mixture was left to stir at room temperature for 16 h, and then concentrated in vacuo. The residue was diluted with CH_2Cl_2 (10 mL) and washed with aqueous $Na_2S_2O_3$ (10 mL) and 1 N NaOH (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give the corresponding 3-aryl-5-iodo-2-pyridone. Selected data: Compound **3a**: Mp: 200–205 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.37 (s, NMe), 3.51 (s, OMe), 3.82 (s, OMe), 6.93 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.62 (s, 1H). Compound **3b**: Mp: 165–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.38 (s, NMe), 3.49 (s, OMe), 7.32–7.47 (m, 5H), 7.69 (s, 1H). Compound **3c**: Mp: 150–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, J = 7.1 Hz, 3H), 3.35 (s, NMe), 3.53 (s, OMe), 4.37 (q, J = 7.1 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.69 (s, 1H), 8.06 (d, J = 8.3 Hz, 2H). Compound **3d**: Mp: 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (s, NMe), 3.51 (s, OMe), 7.48–7.59 (m, 2H), 7.65–7.69 (m, 2H), 7.74 (s, 1H). Compound **3e**: Mp: 138–141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, J = 7.1 Hz, 3H), 3.35 (s, OMe), 4.37 (q, J = 7.1 Hz, 2H), 5.09 (s, 2H), 7.30–7.35 (m, 5H); 7.55 (d, J = 6.7 Hz, 2H), 7.69 (s, 1H), 8.07 (d, J = 6.7 Hz, 2H).
7. *Representative experimental procedure using conventional heating*: A mixture of the 3-aryl-5-iodo-2-pyridone (0.2 mmol), the alkyne (0.6 mmol), $PdCl_2(PPh_3)_2$ (0.02 mmol), and CuI (0.04 mmol) was dissolved in DMF (1 mL) and TEA (2 mL) in a glass tube fitted with a Teflon screw seal. The reactor was flushed with argon, and the reaction mixture was left to stir at 80 °C for 5 days, and then concentrated in vacuo. The residue was purified by column chromatography (silica gel, acetone/CH_2Cl_2) to give the corresponding furopyridone.
8. *Representative experimental procedure using microwave irradiation*: The 3-aryl-5-iodo-2-pyridone (0.2 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol), and CuI (0.01 mmol) were filled into an appropriate small microwave process vial, and were admixed with degassed MeCN (1 mL) and TEA (2 mL). The alkyne (0.22 mmol) was then added, and the vial was sealed with a Teflon septum and placed into a Biotage Initiator™ microwave cavity. After irradiation at 160 °C for 60–150 min and subsequent cooling, the mixture was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, acetone/CH_2Cl_2) to give the corresponding furopyridone.
9. *Analytical data*: Compound **4a**: Solid; Mp: 160–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, NMe); 3.86 (s, OMe), 6.72 (s, 1H), 7.01 (d, J = 8.5 Hz, 2H), 7.34–7.40 (m, 3H), 7.58 (s, 1H), 7.71 (d, J = 7.5 Hz, 2H), 7.92 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.2; 55.3; 98.2; 109.1; 113.5; 115.3; 124.4; 124.9; 127.7; 128.8; 129.1; 129.2; 131.2; 156.8; 158.9; 160.1; 161.4. HRMS (ESI): MH^+, 332.1288; Calcd for $C_{21}H_{17}NO_3$: 332.1287. Compound **4b**: Solid; Mp >205 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, NMe); 3.84 (s, OMe), 3.87 (s, OMe), 6.57 (s, 1H), 6.94 (dd, J = 6.9 and 2.0 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.52 (s, 1H), 7.65 (dd, J = 6.9 and 2.0 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.2; 55.4; 55.5; 96.3; 113.3; 113.5; 114.3; 115.7; 122.0; 124.5; 126.5; 127.1; 131.2; 157.0; 158.9; 160.1; 160.5. HRMS (ESI): MH^+, 362.1392; Calcd for $C_{22}H_{20}NO_4$: 362.1385. Compound **4c**: Solid; Mp >205 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, NMe); 3.88 (s, OMe), 3.93 (s, OMe), 6.85 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.64 (s, 1H), 7.76 (d, J = 8.5 Hz, 2H), 7.92 (d, J = 8.8 Hz, 2H), 8.07 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.4; 52.4; 55.4; 100.6; 109.4; 113.6; 115.0; 124.7; 128.5; 130.2; 130.3; 131.2; 132.0; 133.2; 155.7; 159.1; 166.6. HRMS (ESI): MH^+, 390.1337; Calcd for $C_{23}H_{19}NO_5$: 390.1341. Compound **4d**: Solid; Mp >205 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, NMe), 6.72 (s, 1H), 7.35–7.51 (m, 6H), 7.60 (s, 1H), 7.70–7.73 (m, 2H), 7.95–7.98 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.6; 98.5; 109.8; 115.6; 125.3; 127.9; 128.4; 128.7; 128.8; 129.0; 129.2; 129.5; 129.6; 130.3; 132.4; 132.4; 132.6; 157.3; 160.8; 161.7. HRMS (ESI): MH^+, 302.1181; Calcd for $C_{20}H_{15}NO_2$: 302.1181. Compound **4e**: Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 3H), 4.41 (q, J = 7.1 Hz, 2H), 5.33 (s, 2H), 6.68 (s, 1H), 7.30–7.43 (m, 8H), 7.62 (s, 1H), 7.68 (dd, J = 8.1 and 1.5 Hz, 2H), 8.09 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8; 53.7; 61.3; 98.6; 109.0; 116.0; 116.3; 125.3; 128.6; 128.7; 129.2; 129.3; 129.4; 129.5; 129.6; 129.8; 130.2; 136.9; 137.4; 157.6; 161.0; 162.7; 167.1. HRMS (ESI): MH^+, 450.1705; Calcd for $C_{29}H_{23}NO_4$: 450.1713. Compound **4f**: Solid; Mp: 194–196 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 3H), 3.84 (s, OMe), 4.41 (q, J = 7.1 Hz, 2H), 5.33 (s, 2H), 6.54 (s, 1H), 6.93 (d, J = 8.5 Hz, 2H), 7.32–7.37 (m, 5H), 7.57 (s, 1H), 7.63 (d, J = 8.5 Hz, 2H), 8.09 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8; 53.7; 55.8; 61.3; 96.6; 114.8; 116.3; 122.0; 126.9; 128.0; 128.5; 128.7; 129.4; 129.5; 129.5; 130.2; 137.0; 137.4; 157.8; 161.0; 162.7; 167.1. HRMS (ESI): MH^+, 480.1815; Calcd for $C_{30}H_{26}NO_5$: 480.1811. Compound **4 g**: Solid; Mp: 203–205 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 3H), 3.93 (s, OMe), 4.41 (q, J = 7.1 Hz, 2H), 5.35 (s, 2H), 6.84 (s, 1H), 7.32–7.38 (m, 5H), 7.69 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 8.4 Hz, 4H), 8.16 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8; 52.7; 53.8; 61.4; 101.0; 109.2; 115.6; 125.0; 128.7; 128.8; 129.4; 129.5; 129.6; 130.2; 130.6; 130.8; 133.1; 136.7; 137.1; 150.4; 156.4; 160.9; 166.8; 167.0. HRMS (ESI): MH^+, 508.1761; Calcd for $C_{31}H_{26}NO_6$: 508.1760. Compound **4 h**: Solid; Mp >205 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, J = 7.1 Hz, 3H), 3.69 (s, NMe), 3.82 (s, OMe), 4.39 (q, J = 7.1 Hz, 2H), 6.55 (s, 1H), 6.93 (d, J = 8.7 Hz, 2H), 7.57 (s, 1H), 7.61 (d, J = 8.7 Hz, 2H), 8.08 (d, J = 8.5 Hz, 2H), 8.14 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5; 39.2; 55.5; 61.0; 96.2; 114.4; 115.6; 121.7; 126.5; 128.7; 129.0; 129.2; 129.8; 137.1; 157.2; 160.6; 160.8; 162.4; 166.7. HRMS (ESI): MH^+, 404.1499; Calcd for $C_{24}H_{22}NO_5$: 404.1498. Compound **4i**: Solid; Mp: 183–185 °C. 1H NMR (300 MHz, $CDCl_3$): δ 3.70 (s, NMe), 6.71 (s, 1H), 7.35–7.43 (m, 3H), 7.58–7.62 (m, 3H), 7.66–7.69 (m, 2H), 8.24 (dd, J = 4.0 and 1.8 Hz, 1H), 8.34 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.6; 98.5; 108.0; 115.6; 124.9 (q, J = 271 Hz); 124.4 (q, J = 3.8 Hz); 127.1 (q, J = 3.8 Hz); 129.2; 130.6 (d, J = 32 Hz); 125.2; 128.8; 129.3; 129.6; 129.7; 133.3; 133.4; 157.4; 161.0; 161.4. HRMS (ESI): MH^+, 370.1049; Calcd for $C_{21}H_{14}F_3NO_2$: 370.1055. Compound **4j**: Solid; Mp: 130 °C ^{1}H NMR (300 MHz, CDCl3): δ 0.94 (t, J = 7.1 Hz, 3H), 1.41 (m, 2H), 1.66 (m, 2H), 2.63 (t, J = 7.1 Hz, 2H), 3.68 (s, NMe), 6.10 (s, 1H), 7.50–7.55 (m, 3H), 8.12 (m, 1H), 8.22 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8; 22.3; 27.9; 29.2; 39.1; 98.9; 107.6; 115.1; 122.7; 124.0 (q, J = 3.8 Hz); 126.8 (q, J = 3.8 Hz); 128.1; 128.3; 128.7; 130.0; 130.5; 133.1 (d, J = 32 Hz); 161.0; 161.4. HRMS (ESI): MH^+, 350.1367; Calcd for $C_{19}H_{19}F_3NO_2$: 350.1367.