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Simple and Efficient Large-scale Metal-free Synthesis of *o*-(5-Formyl-2-thienyl)benzonitrile and *o*-(5-Formyl-2-furyl)benzonitrile

Marija Lovrić, Mohamed Majed Tibi, Mirela Filipan, Ivica Cepanec, and Mladen Litvić

BELUPO Pharmaceuticals & Cosmetics Inc., R&D, Ulica Danica 5, 48 000 Koprivnica, Croatia

Organic molecules containing the biaryl motif make up an important class of organic compounds. Many are of natural origin, such as the antibiotic *vancomycin*. Others are valuable drugs for the treatment of hypertension.[1] Some of the drugs containing the biaryl grouping include *valsartan*,[2] *losartan*,[3] *irbesartan*[4] and their congeners. They are among the most prescribed drugs of today. Formation of aryl-aryl bonds has been the subject of numerous papers over the last century[1,5] and several efficient processes for the synthesis of biaryls are available, such as the Ullmann,[6] Suzuki-Miyaura[7] and Negishi reactions.[8]

In connection with our development project on the discovery of drug candidates with thienyl-aryl and furyl-aryl structural features, we required simple and efficient methods for the large scale synthesis of *o*-(5-formyl-2-thienyl)benzonitrile and *o*-(5-formyl-2-furyl)benzonitrile. Currently, reported methods for the preparation of these target compounds or the corresponding intermediates, *o*-(2-thienyl)benzonitrile and *o*-(2-furyl) benzonitrile, employ the Stille coupling from the respective organotin reagents,[9,10] manganese-catalyzed oxidative cross-coupling of Grignard reagents,[11] palladium-catalyzed arylation of thiophene,[12,13] cycloaddition reactions with construction of the thiophene or aryl rings,[14,15] Ullmann condensation of respective aryl iodides[16] and Suzuki-Miyaura reactions.[17,18] However, the main and most important drawbacks of all the published methods are that they are performed on small scale in different solvents at high dilution, use expensive starting materials or toxic or moisture-sensitive reagents. None of the reported methods were convenient for multigram synthesis of the target compounds. We then decided to explore one of the oldest methods for the preparation of such compounds, namely the Gomberg-Bachmann-Hey reaction. An example of the synthesis of *o*-(2-thienyl)benzoic methyl ester (**3b**) by an improved Gomberg-Bachmann-Hey procedure[19] has been tested to afford the product in 41% yield on 3.97 g scale.[16] Somewhat better yields of unsymmetrical biaryls have been obtained under phase-transfer conditions but the method has not been tested in the preparation of our target molecules.[20]

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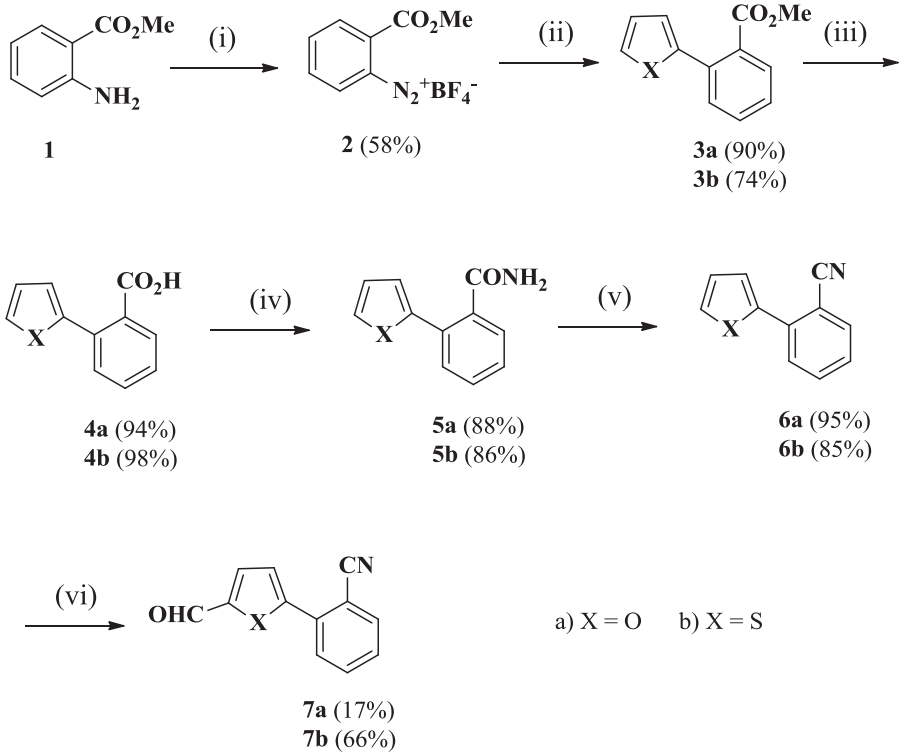
Address correspondence to Marija Lovrić, BELUPO Pharmaceuticals & Cosmetics Inc., Business Development and Regulatory Affairs, I Savica 36, 10 000 Zagreb, Croatia. E-mail: marija.lovric@belupo.hr

This encouraged us to explore this approach further starting from 2-(methoxycarbonyl)benzenediazonium tetrafluoroborate (**2**), employing only potassium acetate as a phase-transfer catalyst in thiophene or furan as solvents and reagents according to *Scheme 1*.[21] After simple work-up of reaction mixtures, the products were isolated by vacuum distillation affording pure **3b** in 74% yield (on 162g scale) and pure **3a** in 90% yield (on a 36.5 g scale) respectively. Work-up of the reaction allows the recovery of excess thiophene and furan as well as of acetonitrile in sufficient purity for further use. The starting 2-(methoxycarbonyl)benzenediazonium tetrafluoroborate (**2**) was prepared from commercially available methyl 2-anthranilate (**1**) by diazotation and subsequent conversion of the resulting diazonium salt to the tetrafluoroborate salt, isolated by filtration.[21–24] The resulting tetrafluoroborate salt **2** was stable in the refrigerator for several months without any trace of decomposition.



(i) HCl, $NaNO_2$, -10°, HBF_4, -5°. (ii) Furan or thiophene; KOAc, 0° - RT, 24 hrs. (iii) OH^-, EtOH, Δ, 1hr. (iv) $COCl_2$, toluene, 1hr, -5°; NH_3, MeOH for **5a** or PCl_5 toluene, 3 hrs, RT, NH_3, MeOH for **5b**. (v) PPE, toluene, Δ, 2 hrs for **6a** or PCl_5, toluene, Δ, 20 hrs, for **6b**. (vi) CH_3OCHCl_2, $SnCl_4$, CH_2Cl_2, -15°, 2 hrs.

Scheme 1

Although the conversion of esters **3a** and **3b** to respective amides **5a** and **5b** is possible by direct ammonolysis reaction with NH_3, it is not easily performed under mild conditions, due to the low reactivity of esters at the *ortho* position to the biaryl bond. Therefore, corresponding esters **3a** and **3b** were hydrolyzed in ethanolic base at room temperature to afford

Table 1
Preparation of *o*-(5-formyl-thiophen-2-yl)benzonitrile (**7b**) and *o*-(5-formyl-furan-2-yl)benzonitrile (**7a**) and respective intermediates

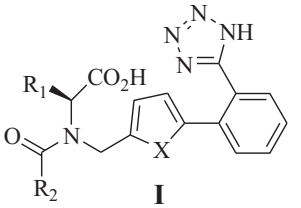
Entry	Product	X	Reagents	Reaction time [h]	Yield [%]	m.p. [°C]	
						Found	Reported
1	**3b**	S	CH_3COOK	20	74.3	Oil	—
2	**3a**	O	CH_3COOK	22	90.3	Oil	—
3	**4b**	S	NaOH	1	98.4	83–86	80,[26] 93–94[27]
4	**4a**	O	KOH	4	94.5	84–86	—
5	**5b**	S	$PCl_5/NH_3/CH_3OH$	24	86.1	140–145	—
6	**5a**	O	$(COCl)_2/NH_3/CH_3OH$	4	87.7	159.5–162.5	—
7	**6b**	S	PCl_5	20	84.8	Oil	—
8	**6a**	O	PPE	1.5	95.2	Oil	—
9	**7a**	S	$CH_3CHCl_2/SnCl_4$	2	65.6	163.5–165.5	161–162[28]
10	**7b**	O	$CH_3CHCl_2/SnCl_4$	1	89.2[a]	135–140	—

[a]Yield after chromatographic purification is 17.2%.

pure acids **4a** and **4b** in nearly quantitative yields. The conversion of acids to amides was successfully performed in a one-pot reaction *via* acyl chlorides and reaction with methanolic ammonia solution. It is interesting to note that a better yield of the acyl chloride in the case of thienyl acid **4b** was obtained with PCl_5, whereas oxalyl chloride was a much better reagent in the case of **4a**. Both amides **5a** and **5b** were obtained in excellent yields after crystallization.

Dehydration of amide **5b** to the corresponding *o*-(2-thienyl)benzonitrile (**6b**) was accomplished in 85% yield by treatment with a slight excess of PCl_5 in refluxing toluene. Acid-sensitive furan derivative **5a** was efficiently converted to *o*-(2-furyl)benzonitrile **6a** with polyphosphate ester (PPE) in toluene at reflux temperature to afford a 95% yield of **6a**. The overall yields of **6a** and **6b** from **1** were 71% and 53% respectively. Finally, the Vilsmeier formylation of **6a** and **6b** was carried out with dichloromethyl methyl ether as formylation agent and tin(IV) chloride as a Lewis acid in dichloromethane at – 15°C for 2 hours. *o*-(5-Formyl-2-thienyl)benzonitrile **7b** was isolated in 66% yield on a 41g scale after crystallization from a diisopropyl ether/acetonitrile mixture (1:1). Acid-sensitive *o*-(5-formyl-furan-2-yl)benzonitrile **7a** was obtained in good yield (89%) under the same conditions. Unlike **7b**, it could not be purified by crystallization due to the presence of tarry material in the crude product. Chromatographic purification gave **7a** in only 17% yield. The low yield is probably caused by the acid sensitivity of the compound **7a** on the silica column. The results presented here represent the first preparation of **7a** in literature. Further work is needed to optimize this step and improve the yield of purified **7a**. The summarized results of the whole synthesis of compounds **7a** and **7b** are presented in *Table 1*.

Both aldehydes **7a** and **7b** have been used for the synthesis of a new series of nonpeptide angiotensin II (AII) receptor antagonists with aryl-thienyl and aryl-furyl segments of the general structure **I**. The results obtained for the synthesis and biological evaluation of compounds of the general structure **I**[21] will be published in due course.



I

X = O, S; R_1 = alkyl, aryl, etc.; R_2 = alkyl

In conclusion, the need for multigram quantities of *o*-(5-formyl-2-thienyl)benzonitrile **7b** and *o*-(5-formyl-furan-2-yl)benzonitrile **7a** starting from simple commercially available chemicals under easily performed reaction conditions in common laboratory glassware makes any organometallic approach to biaryl formation unattractive. Our modification of the Gomberg-Bachmann-Hey reaction was shown to be the best way for biaryl construction starting from the respective diazonium salts **2** in thiophene or furan. The transformation of the resulting intermediates **3b** and **3a** to the target aldehydes **7b** and **7a** was easily performed by using suitable reagents and reaction conditions.

Experimental Section

IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 300 instrument in $CDCl_3$ and D_2O solutions, shifts

are given in δ units ppm downfield from TMS as an internal standard. HPLC analyses were performed with a Thermo Separation Products (San Jose, USA) instrument equipped with vacuum degasser SCM 1000, quaternary gradient pump P 4000, autosampler AS 3000, scanning UV/VIS detector UV 3000 HR and ChromQuest 251 software. TLC analyses were performed on Merck's (Darmstadt, Germany) DC-alufolien with Kieselgel 60_{254}. Column chromatography was carried out on silica gel (particle size ϕ 0.063 – 0.2 mm, Merck). Melting points were determined using a Büchi B540 instrument. Elemental analyses were performed in the Central Analytical Service, at Ruder Bošković Institute, Zagreb, Croatia using a Perkin Elmer 2400 Elemental Analyser. PPE was prepared by the reaction of P_4O_{10} and diethyl ether according to literature method.[25]

2-(Methoxycarbonyl)benzenediazonium Tetrafluoroborate (2)[23]

To a solution of 500 mL conc. hydrochloric acid (37%) and distilled water (500 mL) cooled to 0°C, methyl anthranilate (151 g, 1.0 mol) was added dropwise over 15 min. The reaction mixture was then cooled to −10°C, solid sodium nitrite (70.00 g, 1.01 mol) was added portionwise over 30 min and the mixture was stirred at −10°C for 1 h. Then, urea (1 g) was added at −5°C and after 5 min, 140 mL (1.1 mol) of 50% tetrafluoroboric acid was added dropwise. The reaction mixture was stirred at 0°C for 30 min. The precipitate was collected, washed with distilled water (50 mL) and dried under high vacuum at room temperature to obtain pure **2** as a colorless crystals (144.77 g, 58%), mp 99–102°C. IR (KBr): 3428, 3084, 2282 (N≡N, diazonium group), 1727 (C=O, ester group), 1595 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ 3.97 (s, 3 H), 8.06 (t, $J = 7.4$ Hz, 1 H), 8.25 (t, $J = 7.3$ Hz, 1 H), 8.40 (d, $J = 7.0$ Hz, 1 H), 8.67 (d, J=7.5 Hz, 1 H). ^{13}C NMR (300 MHz, D_2O): δ 67.40 ($O\underline{C}H_3$), 115.03, 131.55, 134.20, 136.24, 137.85, 142.48, 163.15 ($\underline{C}OOCH_3$).

o-*(2-Furyl)benzoic Acid Methyl Ester (3 a)*[29]

To a suspension of 2-(methoxycarbonyl)benzenediazonium tetrafluoroborate (**2**, 50.00 g, 0.2 mol) in furan (360 mL) was added acetonitrile (40 mL). The suspension was cooled to 0°C and potassium acetate (39.26 g, 0.4 mol) was added portionwise over 2 h. The reaction mixture was stirred at 0°C and allowed to come to ambient temperature overnight. Water (1000 mL) was added and the solution was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The oily dark brown residue was distilled under high vacuum to afford pure **3a** as a colorless oil (36.51 g, 90%, bp. 180–183°C/4 mmHg), R_f (dichloromethane) = 0.50. MS (ESI) *m/z* 202.9 $[M+H]^+$. IR (film): 3441, 3148, 3120, 3068, 3028, 2998, 2841, 1729 (C=O, ester group), 1604 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 3 H, $OC\underline{H}_3$), 6.47–6.49 (m, 1 H, Ar), 6.57–6.58 (m, 1 H, Ar), 7.33–7.38 (m, 1 H, Ar), 7.44–7.51 (m, 2 H, Ar), 7.56–7.66 (m, 2 H, Ar). ^{13}C NMR (300 MHz, $CDCl_3$): δ 52.23 ($O\underline{C}H_3$), 107.81, 111.42, 127.50, 127.95, 129.03, 129.66, 129.89, 130.77, 142.61, 152.29, 169.45 ($\underline{C}OOCH_3$).

o-*(2-Thienyl)benzoic Acid Methyl Ester (3b)*[16]

To a suspension of 2-(methoxycarbonyl)benzenediazonium tetrafluoroborate (**2**, 250.00 g, 1.0 mol) in thiophene (2000 mL) was added acetonitrile (200 mL). The suspension was cooled to 0°C and potassium acetate (196.28 g, 2.0 mol) was added

portionwise over 2 h. The reaction mixture was stirred at 10°C and allowed to reach room temperature overnight. The precipitate (potassium tetrafluoroborate) was filtered off and washed with dichloromethane (3 × 200 mL) and the filtrate was evaporated to dryness. The resulting oily dark brown residue was distilled under high vacuum to afford pure **3a** as a pale yellow oil (162.13 g, 74%, bp. 230–233°C/23 mmHg), R_f (dichloromethane) = 0.57. MS (ESI) *m/z* 219.3 $[M+H]^+$. IR (film): 3069, 2950, 1726 (C=O, ester group), 1598, 1571, 1482 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3 H, $OC\underline{H}_3$), 7.02–7.04 (m, 2 H, Ar), 7.45–7.48 (m, 2 H, Ar), 7.31–7.33 (m, 2 H, Ar), 7.69–7.72 (m, 1 H, Ar). ^{13}C NMR (300 MHz, $CDCl_3$): δ 51.92 ($O\underline{C}H_3$), 125.66, 126.08, 126.99, 127.48, 129.21, 130.76, 130.94, 131.55, 133.93, 141.82, 168.85 ($\underline{C}OOCH_3$).

o-*(2-Furyl)benzoic Acid (4a)*[30]

To a solution of *o*-(2-furyl)benzoic acid methyl ester (**3a**, 32.22 g, 0.17 mol) in ethanol (275 mL) was added potassium hydroxide (28.49 g, 0.51 mol). The reaction mixture was heated at reflux temperature for 4 h and concentrated *in vacuo*. The residue was dissolved in water (200 mL) and dichloromethane (200 mL) was added. The resulting biphasic solution was cooled to 10°C and hydrochloric acid (37%, 50 mL, 59.25 g solution, 21.93 g HCl, 0.6 mol) was added dropwise during 30 min. The phases were separated and the aqueous phase was additionally extracted with dichloromethane (2 × 50 mL). Organic layers were collected, dried over Na_2SO_4, filtered and evaporated to afford pure **4a** as pale brown oily crystals (30.08 g, 95%), mp 84–86°C, (*lit.*[30] 87°C), R_f (dichloromethane/methanol 9/1) = 0.44. MS (ESI) *m/z* 211.8 $[M+Na]^+$. IR (KBr): 3855, 3840, 3819, 3691, 3673, 3650, 3121, 2817, 2659, 2550, 1688 (C=O, carboxyl group), 1605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.45–6.47 (m, 1 H, Ar), 6.63–6.64 (m, 1 H, Ar), 7.34–7.39 (m, 1 H, Ar), 7.48–7.55 (m, 2 H, Ar), 7.58–7.61 (m, 1 H, Ar), 7.83–7.86 (m, 1 H, Ar), 12.16 (s, 1 H, $COO\underline{H}$). ^{13}C NMR (300 MHz, $CDCl_3$): δ 108.33, 111.37, 127.56, 128.58, 128.71, 129.99, 130.58, 131.73, 142.75, 152.02, 174.45 ($\underline{C}OOH$).

o-*(2-Thienyl)benzoic Acid (4b)*

To a solution of *o*-(2-thienyl)benzoic acid methyl ester (**3b**, 160.00 g, 0.7 mol) in ethanol (1300 mL) was added sodium hydroxide (44.00 g, 1.1 mol). The reaction mixture was heated at reflux temperature for 1 h and concentrated *in vacuo*. The residue was dissolved in distilled water (800 mL) and cooled to 10°C. Hydrochloric acid (37%, 100 mL, 118.50 g solution, 43.85 g HCl, 1.2 mol) was added dropwise over 30 min. The mixture was extracted with chloroform (1 × 600 mL, 2 × 200 mL). Organic layers were collected, dried over Na_2SO_4, filtered and evaporated to afford pure **4b** as a pale yellow crystals (147.30 g, 98%), mp 83–86°C, (*lit.*[6] 80°C, *lit.*[13] 93–94°C), R_f (dichloromethane/methanol 9/1) = 0.36. MS (ESI) *m/z* 227.9 $[M+Na]^+$. IR (KBr): 3818, 3734, 3648, 2922, 2353, 1687 (C=O, carboxyl group), 1594 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.09–7.15 (m, 2 H, Ar), 7.37–7.52 (m, 2 H, Ar), 7.53–7.60 (m, 2 H, Ar), 7.94–8.01 (m, 1 H, Ar), 11.82 (s, 1 H, $COO\underline{H}$). ^{13}C NMR (300 MHz, $CDCl_3$): δ 125.91, 126.61, 127.09, 127.60, 129.96, 130.62, 131.63, 131.76, 134.95, 141.38, 173.86 ($\underline{C}OOH$).

o-*(2-Furyl)benzamide (5a)*

To a solution of *o*-(2-furyl)benzoic acid (**4a**, 30.00 g, 0.16 mol) in toluene (225 mL) and dimethylformamide (DMF, 1 mL) previously cooled to −5°C oxalyl chloride (15 mL,

22.2 g, 0.18 mol) was added dropwise over 15 min. The mixture was further stirred for 1 h. The obtained pale brown solution was added dropwise to ammonia solution in methanol (27.0 g, 225 mL, 1.59 mol) cooled to −10°C over 20 min. The reaction mixture was stirred at 0°C for another 2 h and allowed to reach room temperature overnight. The suspension was concentrated *in vacuo*, the residue was diluted with distilled water (600 mL) and extracted with ethyl acetate (1 × 900 mL, 3 × 450 mL). Organic layers were collected, dried over Na_2SO_4, filtered and evaporated to dryness. Crude product was recrystallized from diisopropyl ether (110 mL), filtered and dried to afford pure **5a** as pale brown crystals (26.18 g, 88%), mp 159.5–162.5°C, R_f (dichloromethane/2-propanol/acetic acid 9.5/0.5/0.1) = 0.42. MS (ESI) *m/z* 188.0 $[M+H]^+$. IR (KBr): 3392 (N-H, amide group), 3288, 3180 (N-H, amide group), 3126, 1644 (C=O, amide group), 1622 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.88 (s, 2 H, N<u>H</u>$_2$), 6.49–6.52 (m, 1 H, Ar), 6.78–6.79 (m, 1 H, Ar), 7.34–7.37 (m, 1 H, Ar), 7.41–7.42 (m, 1 H, Ar), 7.44–7.45 (m, 1 H, Ar), 7.57–7.57 (m, 1 H, Ar), 7.72–7.75 (m, 1 H, Ar). ^{13}C NMR (300 MHz, $CDCl_3$): δ 109.48, 112.83, 127.75, 128.58, 128.81, 129.28, 130.90, 135.41, 144.00, 153.10, 176.16 (N–<u>C</u>=O, amide group).

Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.50; H, 4.80; N, 7.55.

o-*(2-Thienyl)benzamide (5b)*

To a suspension of phosphorus pentachloride (154.15 g, 0.74 mol) in toluene (720 mL) *o*-(2-thienyl)benzoic acid (**4b**, 144.00 g, 0.71 mol) was added portionwise at 0°C over 1 h. The reaction mixture was stirred at 3°C to room temperature for 3 h. The obtained pale brown toluene solution was added dropwise to ammonia solution in methanol (150.0 g, 1450 mL, 8.82 mol) cooled to −10°C over 3 h. The reaction mixture was stirred at 0°C for another 2 h and allowed to reach room temperature overnight. The suspension was concentrated *in vacuo*, the residue was diluted with distilled water (2500 mL) and extracted with dichloromethane (1 × 1500 mL, 2 × 250 mL). Organic layers were collected, dried over Na_2SO_4, filtered and evaporated to dryness. Crude product was heated at reflux temperature in *n*-hexane (600 mL) overnight. After cooling the product was filtered, washed with *n*-hexane (2 × 50 mL) and dried to give pure **5b** as a pale brown crystals (123.38 g, 86%), mp 140–145°C, R_f (dichloromethane/methanol/triethylamine 9/1/0.1) = 0.65. MS (ESI) *m/z* 204.1 $[M+H]^+$. IR (KBr): 3370 (N-H, amide group), 3172 (N-H, amide group), 1698 (C=O, amide group), 1639, 1621 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.64 (s, 1 H, N<u>H</u>$_2$), 6.16 (s, 1 H, N<u>H</u>$_2$), 7.07 (s, 1 H, Ar), 7.19 (s, 1 H, Ar), 7.26–7.45 (m, 4 H, Ar), 7.65 (d, 1 H, Ar, *J*=7.6 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 126.34, 126.99, 127.65, 127.91, 128.52, 130.11, 130.63, 131.78, 134.93, 140.83, 171.40 (N–<u>C</u>=O, amide group).

Anal. Calcd for $C_{11}H_9NOS$: C, 65.00; H, 4.46; N, 6.89. Found: C, 64.92; H, 4.39; N, 6.92.

o-*(2-Furyl)benzonitrile (6 a)*

To a suspension of ethyl polyphosphate (52.6 g) in toluene (105 mL) *o*-(2-furyl)benzamide (**5a**, 26.13 g, 0.14 mol) was added portionwise at room temperature. The reaction mixture was heated at reflux temperature for 2 h, cooled to room temperature and diluted with water (200 mL). Layers were separated and the aqueous phase was extracted with toluene (2 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered

and evaporated to afford pure **6a** as a brown oil (22.47 g, 95%,), R_f (dichloromethane) = 0.72. MS (ESI) *m/z* 169.97 $[M+H]^+$. IR (film): 3121, 3027, 2985, 2913, 2224 (C≡N), 1599, 1567 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.55 (d, 1 H, Ar, J=1.6 Hz), 7.27–7.33 (m, 2 H, Ar), 7.55 (s, 1 H, Ar), 7.59–7.61 (m, 1 H, Ar), 7.68 (d, 1 H, Ar, J=7.7 Hz), 7.87 (d, 1 H, Ar, J=8.0 Hz). ^{13}C NMR (300 MHz, $CDCl_3$,): δ 106.55 (C≡N), 110.20, 112.02, 118.77, 125.69, 126.90, 132.74, 132.95, 133.90, 143.12, 149.52.

Anal. Calcd for $C_{11}H_7NO$: C, 78.09; H, 4.17; N, 8.28. Found: C, 78.14; H, 4.11; N, 8.30.

o-*(2-Thienyl)benzonitrile (6b)*

To a suspension of phosphorus pentachloride (131.19 g, 0.63 mol) in toluene (850 mL) *o*-(2-thienyl)benzamide (**5b**, 121.96 g, 0.60 mol) was added portionwise at room temperature over 20 min. The reaction mixture was heated at reflux temperature overnight, cooled to room temperature and diluted with mixture of ice and water (2400 mL). Layers were separated and the aqueous phase was extracted with toluene (2 × 300 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to afford pure **6b** as a pale brown oil (94.26 g, 85%,), R_f (dichloromethane) = 0.65. MS (ESI) *m/z* 186.04 $[M+H]^+$. IR (film): 3107, 2224 (C≡N), 1708, 1595 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.12–7.14 (m, 1 H, Ar), 7.33–7.36 (m, 1 H, Ar), 7.40–7.41 (m, 1 H, Ar), 7.54–7.62 (m, 3 H, Ar), 7.69–7.70 (m, 1 H, Ar). ^{13}C NMR (300 MHz, $CDCl_3$): δ 109.76 (C≡N), 118.56, 127.08, 127.31, 127.34, 127.96, 129.42, 132.71, 134.02, 137.27, 139.18.

Anal. Calcd for $C_{11}H_7NS$: C, 71.32; H, 3.81; N, 7.56. Found: C, 71.37; H, 3.72; N, 7.50.

o-*(5-Formyl-2-Furyl)benzonitrile (7a)*

To a solution of *o*-(2-furyl)benzonitrile (**6a**, 20.46 g, 0.12 mol) in dichloromethane (120 mL) cooled at −15°C was added dropwise a solution of dichloromethyl methyl eter (16.1 mL, 20.85 g, 0.18 mol) in dichloromethane (40 mL). Then, tin(IV) chloride solution in dichloromethane (21.2 mL, 47.25 g, 0.18 mol) was added dropwise over 1 h. The reaction mixture was stirred at −15°C for 1 h and after distilled water (300 mL) and dichloromethane (100 mL) were added the mixture was vigorously stirred using a mechanical stirrer for another 30 min. Layers were separated and the water layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated *in vacuo* to afford crude **7a** as a dark tarry material (21.38 g, 89.2%). The crude product was purified by column chromatography (dichloromethane) to give pure **7a** as a pale orange to brown crystals (4.12 g, 17%), mp 136–140°C, R_f (dichloromethane) = 0.30. MS (ESI) *m/z* 198.04 $[M+H]^+$. IR (KBr): 2923, 2854, 2221 (C≡N), 1735, 1682 (C=O, aldehyde group), 1665, 1596 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, 1 H, Ar, J=3.8 Hz), 7.52–7.54 (m, 2 H, Ar.), 7.70–7.75 (m, 1 H, Ar), 7.78–7.81 (m, 1 H, Ar), 8.12 (d, 1 H, Ar, J=8.1 Hz), 9.75 (s, 1 H, CHO). ^{13}C NMR (300 MHz, $CDCl_3$): δ 108.39 (C≡N), 112.27, 118.22, 122.72, 127.23, 129.18, 131.30, 133.16, 134.26, 152.15, 154.19, 177.51 (CHO).

Anal. Calcd for $C_{12}H_7NO_2$: C, 73.09; H, 3.58; N, 7.10. Found: C, 73.13; H, 3.61; N, 7.06.

o-*(5-Formyl-2-Thienyl)benzonitrile (7b)*[16]

To a solution of *o*-(2-thienyl)benzonitrile (**6b**, 55.00 g, 0.30 mol) in dichloromethane (280 mL) cooled at −15°C was added dropwise a solution of dichloromethyl methyl eter (39.5 mL, 51.18 g, 0.44 mol) in dichloromethane (150 mL). Then, tin(IV) chloride solution in dichloromethane (52 mL, 115.92 g, 0.44 mol) was added dropwise over 20 min. The reaction mixture was stirred at −15°C for 2 h and after distilled water (500 mL) and dichloromethane (300 mL) were added the mixture was vigorously stirred using a mechanical stirrer for another 30 min. Layers were separated and water layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated *in vacuo* to afford crude **7b** as a dark solid (66.52 g, 105%). Crude product was heated at reflux temperature in diisopropyl ether/acetonitrile mixture (1:1, 420 mL) during 1 h. After cooling at −10°C for 2 h the product was filtered, washed with diisopropyl ether/acetonitrile mixture (3 × 30 mL) and dried to give pure **7b** as a pale brown crystals (41.56 g, 66%), mp 163.5–165.5°C, (*lit.*[16] 161–162°C), R_f (dichloromethane) = 0.34. MS (ESI) *m/z* 214.1 $[M+H]^+$. IR (KB): 3096, 3066, 3031, 2922, 2853, 2833, 2814, 2759, 2220 (C≡N), 1672 (C = O, aldehyde group), 1593 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.51–7.54 (m, 1 H, Ar), 7.68–7.69 (m, 3 H, Ar), 7.80–7.82 (m, 2 H, Ar), 9.95 (s, 1 H, C<u>H</u>O). ^{13}C NMR (300 MHz, $CDCl_3$): δ 110.49 (<u>C</u>≡N), 128.35, 129.08, 129.84, 133.16, 134.38, 136.57, 144.49, 148.36, 182.65 (<u>C</u>HO).

Anal. Calcd for $C_{12}H_7NOS$: C, 67.58; H, 3.31; N, 6.57. Found: C, 67.50; H, 3.35; N, 6.50.

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References

1. I. Cepanec, *Synthesis of Biaryls*. Amsterdam: Elsevier, 2004.
2. A. Markham and K. L. Goa, *Drugs*, **54**, 299 (1997).
3. D. J. Carini, J. V. Duncia, P. E. Aldrich, A. T. Chiu, A. L. Johnson, M. E. Pierce, W. A. Price, J. B. Santella, G. J. Wells, R. R. Wexler, P. C. Wong, S. Yoo and P. B. M. Timmermans, *J. Med. Chem.*, **34**, 2525 (1991).
4. B. Christophe, R. Libon, C. Cazaubon, D. Nisato, A. Manning and P. Chatelain, *Eur. J. Pharm.*, **281**, 161 (1995).
5. J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, **102**, 1359 (2002).
6. F. Ullmann, *Ber.*, **29**, 1878 (1896).
7. N. Miyaura and A. Suzuki, *Chem. Rev.*, **95**, 2457 (1995).
8. E. Negishi, A. O. King and N. Okukado, *J. Org. Chem.*, **42**, 1821 (1977).
9. J. R. Naber and S. L. Buchwald, *Adv. Synth. Catal.*, **350**, 957 (2008).
10. F. Delgado, J. Pastor, J. L. Garcia-Navio, J. J. Vaquero and J. Alvarez-Builla, *Farmaco*, **52**, 147 (1997).
11. G. Cahiez, C. Duplais and J. Buendia, *Angew. Chem. Int. Ed.*, **48**, 6731 (2009).

12. R. Roger, F. Požgana and H. Doucet, *Green Chem.*, **11**, 425 (2009).

13. B. Glover, K. A. Harvey, B. Liu, M. J. Sharp and M. F. Tymoschenko, *Org. Lett.*, **5**, 301 (2003).

14. H. Gotthard, C. M. Weisshuhn and B. Christl, *Liebigs Ann. Chem.*, **360** (1979).

15. B. Sain and J. S. Sandhu, *J. Org. Chem.*, **55**, 2545 (1990).

16. S. Mataka, T. Ohshima and M. Tashiro, *J. Org. Chem.*, **46**, 3960 (1981).

17. V. Pomel, J. Klicic, D. Covini, D. D. Church, J. P. Shaw, K. Roulin, F. Burgat-Charvillon, D. Valognes, M. Camps, C. Chabert, C. Gillieron, B. Francon, D. Perrin, D. Leroy, D. Gretener, A. Nichols, P. A. Vitte, S. Carboni, C. Rommel, M. K. Schwarza and T. Ruckle, *J. Med. Chem.*, **49**, 3857 (2006).

18. D. N. Korolev and N. A. Bumagin, *Tetrahedron Lett.*, **47**, 4225 (2006).

19. G. Fukata, K. Kawazoe and T. Taguchi, Yakugaku Zasshi, **94**, 852 (1974). *Chem. Abstr.*, **81**, 120124 (1974).

20. J. R. Beadle, S. H. Korzeniowski, D. E. Rosenberg, B. J. Garcia-Slanga and G. W. Gokel, *J. Org. Chem.*, **49**, 1594 (1984).

21. M. Lovrić, *Synthesis and Biological Evaluation of Novel Biaryl Compounds*, Ph.D. Thesis, University of Zagreb, 2007.

22. A. Roe, *Org. React.*, **5**, 193 (1949).

23. I. Cepanec, M. Litvić, J. Udiković, I. Pogorelić and M. Lovrić, *Tetrahedron*, **63**, 5614 (2007).

24. S. R. Sandler and W. Karo, *Organic Functional Group Preparations*, 2nd ed., Vol. I, New York, NY: Academic, 1983.

25. F. S. Falsone and C. O. Kappe, *Arkivoc*, **122** (2001).

26. B. M. Jr York, US Patent 5070100, 1991.

27. A. W. Chow, N. M. Hall, J. R. E. Hoover, M. M. Dolan and R. J. Ferlauto, *J. Med. Chem.*, **9**, 551 (1966).

28. F. Delgado, J. Pastor, J. L. Garcia-Navio, J. J. Vaquero and J. Alvarez-Builla, *Farmaco*, **52**, 147 (1997).

29. Y. Kobayashi, A. D. William and R. Mizojiri, *J. Organometall. Chem.*, **653**, 91 (2002).

30. J. Charton, S. Girault-Mizzi, M. A. Debreu-Fontaine, F. Foufelle, I. Hainault, J. G. Bizot-Espiard, D. H. Caignard and C. Sergheraert, *C. Bioorg. Med. Chem.*, **14**, 4490 (2006).