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Microwave-promoted Heck and Suzuki coupling reactions of new 3-(5-bromobenzofuranyl)pyrazole in aqueous media

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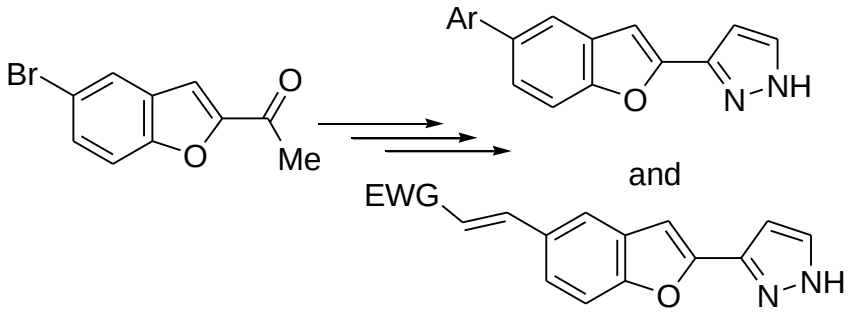
Abstract

Suzuki-Miyaura and Mizoroki-Heck cross-coupling reactions of 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole with various arylboronic acids and terminal olefins, respectively, were investigated using a benzothiazole-oxime palladium(II) complex, under both thermal and microwave-irradiation conditions, in an open vessel, using aqueous solvent. The benzothiazole-oxime-based Pd(II) complex was found to be an efficient, and highly active pre-catalyst for the cross-coupling reactions, and for the preparation of new C-C cross-coupled compounds of potential biological interest which are difficult to obtain using other synthetic routes.



Keywords: Benzofurans, pyrazoles, palladium catalysis, microwave, C-C cross couplings.

Introduction

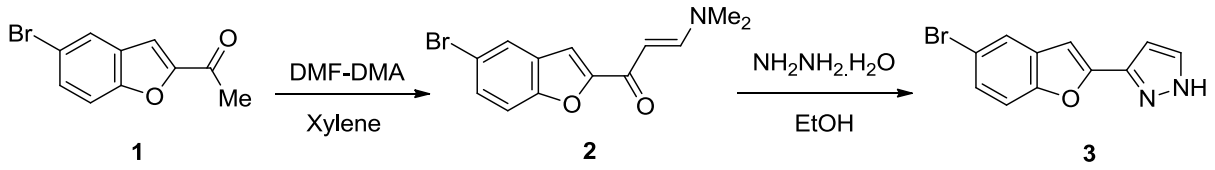
The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction represents one of the most widely used processes for arylation of aromatic and heteroaromatic compounds.[1–6] In addition, palladium-catalyzed Heck reactions of aryl halides with alkenes are one of the most powerful tools in organic synthesis for the construction of carbon–carbon bonds.[7–10] Interestingly, growing research work is focused on the use of microwave-irradiation methodology as a heating source because it markedly assists in achieving rapid incorporation of organic synthesis into diverse industrial applications.[11–14] Furthermore, organic reactions that proceed well in aqueous media have several advantages over those that take place in organic solvents.[15–17]

The benzofuran moiety constitutes the core of several pharmaceutically-active natural products, such as *Cicerfuran, Conocarpan, Ailanthoidol*, *Amiodarone* and *Bufuralol*.[18–22] The synthetic benzofuran derivatives are reported to be effective drugs which have huge medicinal applications. [23–26] Pyrazolylbenzofuran derivatives, for example, have proven to have potent cytotoxic,[27] antimicrobial,[28–30] antioxidant[31] and insecticidal[32] activities.

In continuation of our research work on the use of palladium(II) complexes under microwave irradiation for Suzuki–Miyaura, Heck–Mizoroki, and Sonogashira cross-coupling reactions,[33–44] we report, herein, the use of the benzothiazole-oxime palladium(II) complex (**4**) as a pre-catalyst for the Suzuki–Miyaura and Heck–Mizoroki cross-coupling reactions of 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (**3**) under thermal heating and microwave irradiation in aqueous media.

Results and Discussion

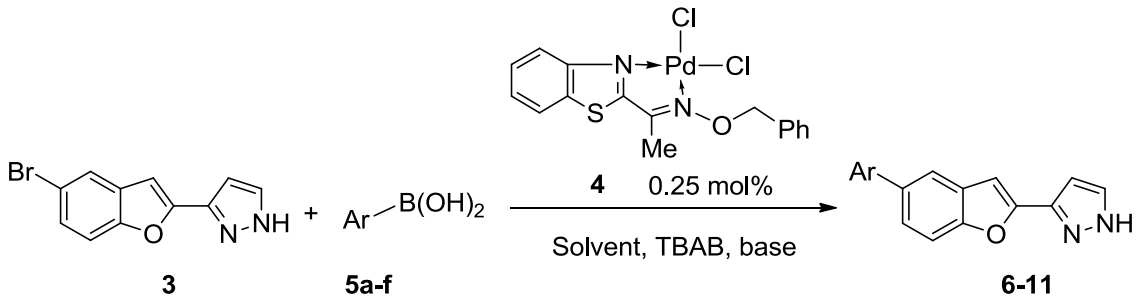
1-(5-Bromobenzofuran-2-yl)ethanone (**1**) was first prepared following a procedure reported in the literature.[45] Treatment of **1** with dimethylformamide-dimethylacetal (DMF-DMA) in dry xylene at reflux temperature afforded (*E*)-1-(5-bromobenzofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one (**2**).[46] The enaminone derivative **2** was then reacted with hydrazine hydrate in refluxing ethanol to give 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (**3**) as shown in Scheme 1.[46] The structures of the new 5-bromobenzofuran derivatives (**2**) and (**3**) were confirmed from their elemental analyses and spectroscopic data (IR, MS, ^{1}H and ^{13}C NMR). The *E*-configuration of structure **2** was established based on the coupling constant *J* of 12.6 Hz.



Scheme 1. Synthesis of 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (**3**).

Suzuki cross-coupling of 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (3) with arylboronic acids (5a-f) under thermal heating and microwave irradiation

The catalytic activity of the Pd(II)-complex (**4**) (0.25 mol%) in the Suzuki-Miyaura cross-coupling reaction of a novel candidate, 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (**3**), with arylboronic acids **(5a-f**) has been examined (Scheme 2).



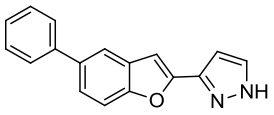
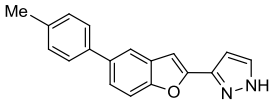
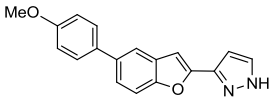
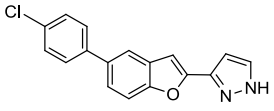
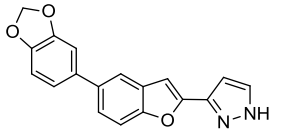
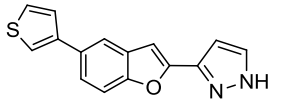
Scheme 2. Suzuki cross-coupling of 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (**3**) with arylboronic acids (**5a-f**) under thermal and μw conditions.

First, the catalytic condition [water/tetrabutylammonium bromide (TBAB)/KOH] was applied for the coupling of the 5-bromobenzofuran derivative (**3**) with phenylboronic acid (**5a**). No reaction was observed, however, after 15 min of microwave irradiation (μw) or 6 h of thermal heating (entry 1, Table 1). Repeating the same reaction in DMF instead of water using Et_3N and TBAB under μw irradiation for 20 min gave 3-(5-phenylbenzofuran-2-yl)-1*H*-pyrazole (**6**) in 70% isolated yield (entry 2, Table 1). Next, the solvent mixture of water-DMF (1:1, v/v) was applied using KOH and TBAB under thermal heating for 6 h as well as under μw irradiation for 20 min. Under these conditions, full conversions were observed (based on TLC) with 90% and 88% isolated yields, respectively, to 3-(5-phenylbenzofuran-2-yl)-1*H*-pyrazole (**6**) (entry 3, Table 1).

The above reaction conditions were applied for further Suzuki-Miyaura cross-coupling reactions of the bromide (**3**) with aryl and heteroarylboronic acids (**5b-f**). The reaction-components molar ratios, in all cases, were: 1 mmol of bromide, 1.2 mmol of the arylboronic acids, 0.6 mmol TBAB, 2 mmoles of KOH and 0.25 mol% of the complex (**4**) in a water-DMF mixture (1:1, v/v) (3 mL). The arylboronic acids were coupled, accordingly, with the bromide (**3**) under thermal heating as well as microwave irradiation to give the corresponding arylated benzofuran products (**7-11**) in very good isolated yields (Table 1). The only exception was the coupling of bromide (**3)** with 2-thienylboronic acid (**5f)**, in which the reaction did not proceed at all when water-DMF/TBAB/KOH was used (entry 8, Table 1). Therefore, KOH was replaced with cesium carbonate, a more reactive base. Using Cs_2CO_3 and 0.5 mol% of Pd-pre-catalyst (**4**), reasonable yields were obtained after 30 min of μw irradiation (53%), and after 14 h of thermal heating (42%), respectively (entry 9, Table 1).

Although, the microwave irradiation reaction times were generally ~ 20-25 min, the corresponding coupled products (**6-10**) were isolated mostly in high yields (~ 73-88%) as shown in Table 1. A rationale for the long reaction time required to accomplish C-C cross-coupling of bromide (**3**) might be due to the presence of two π-electron-excessive heterocycles (pyrazole and furan) in **3**. Therefore, even though the 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (**3**) is considered to be a deactivated bromide, the full conversion of **3** in water-DMF using 0.25 mol% of the pre-catalyst (**4**) reflects the high catalytic activity of this catalyst. The structures of the cross-coupled products were confirmed by spectral data (^{1}H and ^{13}C NMR, MS and IR) and elemental analyses, as reported in the experimental section.

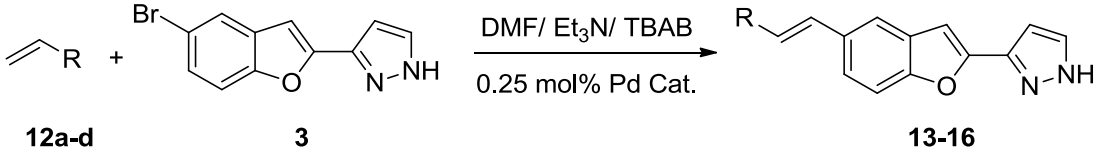
Table 1. Results of Suzuki cross-coupling of 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (**3**) with arylboronic acids (**5a-f)** under thermal and μw conditions

Entry	Product	Solvent	Thermal heating[a,b]		μw heating[a,b]	
			Time (h)	Yield%	Time (min)	Yield%
1	 **6**	H_2O/ KOH	6	0	15	0
2		DMF/ TEA	-	-	20	70
3		H_2O-DMF/ KOH	6	90	20	88
4	 **7**	H_2O-DMF/ KOH	8	80	25	84
5	 **8**	H_2O-DMF/ KOH	8	72	25	80
6	 **9**	H_2O-DMF/ KOH	6	95	20	87
7	 **10**	H_2O-DMF/ KOH	8	70[c]	25	73[c]
8	 **11**	H_2O-DMF/ KOH	6	0	20	0
9		H_2O-DMF/Cs_2CO_3	14	42[c]	30	53[c]

[a]Conditions. Bromide: 1 mmol; arylboronic acid: 1.2 mmol; TBAB: 0.6 mmol; base: 2 mmol; water or DMF: 3 mL, water-DMF: 3 mL (1:1, v/v), Pd-complex: 0.25 mol%, microwave heating (250 Watt) at 160 ºC and at reflux for thermal heating. [b]The values of yield% refer to the isolated yields. [c]The starting substrate (**3**) was detected by TLC.

Heck cross-coupling of 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (3) with olefins (12a-d)

The potential of the Pd-complex (**4**) towards Heck cross-coupling of the olefins (**12a-d)** with 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole **(3)** under both microwave and thermal heating was studied (Scheme 3).



Scheme 3. Heck cross-coupling reactions of 3-(5-bromobenzofuran-2-yl)-*1H*-pyrazole (**3**) with olefins **12a-d** under thermal and μw conditions.

In all cases, full conversions into the corresponding disubstituted olefins **(13-16**) were confirmed by high isolated yields (Table 2). Styrene (**12a**) was easily coupled with the 5-bromobenzofuran (**3)** in the presence of

0.25 mol% of the Pd-complex (**4)** using DMF/Et_3N/TBAB as the catalytic system, to afford the 5-styrylbenzofuran derivative (**13)** in excellent yield (entry 1, Table 2) after 8 hours of thermal heating or 20 min of microwave irradiation. In a similar trend, 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (**3**) cross-coupled with acrylonitrile, ethyl acrylate, and *n*-butyl acrylate, respectively, under similar catalytic conditions, resulting in full conversions into the corresponding pyrazolyl benzofuranyl acrylates (**14-16)** under both thermal and microwave heating conditions.

Table 2. Results of Heck cross-coupling reactions of 3-(5-bromobenzofuran-2-yl)-*1H*-pyrazole (**3**) with olefins (**12a-d**) under thermal and μw conditions

Entry	Olefins		Product	Thermal heating[a,b]	μw heating[a,b]
	No.	R		Yield%	Yield%
1	**12a**	Ph	**13**	84	87
2	**12b**	CN	**14**	79	82
3	**12c**	CO_2Et	**15**	94	90
4	**12d**	CO_2Bu^n	**16**	91	85

[a]Conditions. Bromide: 1 mmol; olefin: 1.5 mmol; TBAB: 0.6 mmol; Et_3N: 3 mmol; DMF: 3 mL, Pd-complex: 0.25 mol%, microwave heating (250 Watt) at 160 ºC for 20 min, and thermal heating at 130 ºC for 8 h. [b]The values of yield% refer to the isolated yields.

In all cases, the cross-coupling reaction was highly regio- and stereoselective, yielding only the *E*-isomer of the disubstituted olefins **13-16**, as substantiated by the GC, GC-MS and ^{1}H NMR-spectra of the crude reaction mixtures. The structures of the new products were confirmed from their elemental and spectral analyses. The *trans*-configuration of the products was estimated from spectral data, in which the butyl acrylate derivative **(16**) showed, for example, two characteristic doublets at δ 6.62 and 7.76 ppm with coupling constant *J* value 15.9 Hz, respectively, in its ^{1}H NMR spectrum.

Conclusions

In conclusion, the benzothiazole-oxime-based Palladium(II) complex (**4**) was found to be an efficient and highly active pre-catalyst for Suzuki-Miyaura and Heck-Mizoroki cross-coupling reactions of deactivated 3-(5-bromobenzofuran-2-yl)-*1H*-pyrazole (**3**) in aqueous medium, under thermal heating and microwave-irradiation conditions, for the preparation of new C-C cross-coupled products which are of potential biological and therapeutic interest and are difficult to obtain by other synthetic routes.

Experimental Section

General. Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimaduz FTIR 8101 PC

infrared spectrophotometer. NMR spectra were recorded using a Varian Mercury VXR-300 NMR spectrometer at 300 MHz (^{1}H NMR) and at 75 MHz (^{13}C NMR) using DMSO-d_6 as solvent. Capillary GC analyses were performed with a Shimadzu GC-14A or GC-14B, a Shimadzu C-R6A Integrator, and a HP 5 column (25 m length, 0.25 mm i.d., 0.25 μm film) or recorded with an Agilent GC 6890N. Mass spectra (EI) were obtained at 70 eV using a type Shimadzu GCMQP 1000 EX Spectrometer. Analytical thin-layer chromatography (TLC) was performed using pre-coated silica gel 60778 plates (Fluka), and the spots were visualized with UV light at 254 nm. Fluka silica gel 60741 (70-230 mesh) was used for flash column chromatography. Microwave experiments were carried out using a CEM Discover Labmate™ Microwave (300 W with ChemDriver™ Software). The palladium complex (**4**) was prepared following our procedure previously reported in the literature.[38]

Synthesis of (*E*)-1-(5-bromobenzofuran-2-yl)-3-(dimethylamino)-prop-2-en-1-one (2). A mixture of 1-(5-bromobenzofuran-2-yl)ethanone **(1)** (4.78 g, 20 mmol) and dimethyl formamide-dimethylacetal (DMF-DMA) (2.66 ml, 20 mmol) was taken up in dried xylene (20 ml). The mixture was refluxed for 8 h, then left to cool to room temperature. The reddish-brown precipitated product was filtered off, washed with petroleum ether (60/80 ^{o}C), and dried. Recrystallization of the precipitate from benzene afforded 5.17 g of (*E*)-1-(5-bromobenzofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one **(2)** (88% yield), mp 148-150 ^{o}C; IR (KBr) υ 3434, 3100, 2915, 1638, 1566, 1539, 1353, 1109 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 2.94 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 5.81 (d, 1H, *J* 12.6 Hz, CH olefinic), 7.48 (s, 1H, CH aromatic), 7.54 (d, 1H, *J* 8.7 Hz, CH aromatic), 7.64 (d, 1H, *J* 8.7 Hz, CH aromatic), 7.81 (d, 1H, *J* 12.6 Hz, CH olefinic), 7.93 (s, 1H, CH aromatic); ^{13}C NMR (75 MHz, DMSO-d_6) δ 37.2, 44.6, 90.9, 107.8, 113.8, 115.5, 124.7, 128.9, 129.7, 153.0, 154.1, 156.5, 175.4; MS *m/z* (%) 294 (24.2, M^+), 276 (18.7), 167 (25.3), 98 (58.2), 88 (40.7), 70 (57.1), 55 (100). Anal. Calcd for $C_{13}H_{12}BrNO_2$: C, 53.08; H, 4.11; N, 4.76. Found: C, 53.10; H, 4.07; N, 4.69%.

Synthesis of 3-(5-bromobenzofuran-2-yl)-*1H*-pyrazole (3). Hydrazine hydrate (2 ml) was added to a stirred solution of the 3-(dimethylamino)prop-2-en-1-one (**2**) (2.94, 10 mmol) in acetic acid (30 ml). Stirring was continued overnight at room temperature and the solid product obtained was filtered off, washed with ethanol, dried and recrystallized from DMF to afford 2.23 g (85% yield) of 3-(5-bromobenzofuran-2-yl)-1H-pyrazole (**3**) as yellow crystals; mp. 204-206 ^{o}C; IR (KBr) υ 3511, 3126, 2913, 1536, 1412, 1044 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.76 (d, 1H, *J* = 2.1 Hz, CH aromatic), 7.14 (s, 1H, CH aromatic), 7.41 (d, 1H, *J* 8.7 Hz, CH aromatic), 7.59 (d, 1H, *J* 8.7 Hz, CH aromatic), 7.84 (s, 1H, CH aromatic), 7.88 (s, 1H, CH aromatic), 13.25 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 100.8, 103.2, 112.9, 115.3, 120.7, 123.3, 126.6, 130.0, 130.8, 131.8, 152.6; MS *m/z* (%) 263 (100, M^+), 184 (24.7), 156 (31.2), 128 (37.7), 101 (58.4), 75 (76.6), 62 (87). Anal. Calcd for $C_{11}H_7BrN_2O$: C, 50.22; H, 2.68; N, 10.65. Found: C, 50.26; H, 2.61; N, 10.62%.

Suzuki cross-coupling reactions of 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (3) with arylboronic acids in water-DMF under thermal heating. General procedure. A mixture of 3-(5-bromobenzofuran-2-yl)-*1H*-pyrazole (**3**) (263 mg, 1 mmol), and the appropriate arylboronic acids (**5a-f**) (1.2 mmol), tetrabutylammonium bromide (TBAB) (194 mg, 0.6 mmol), palladium complex (**4**) (1.14 mg, 0.25 mol %), KOH (112 mg, 2 mmol), and water-DMF (1:1) (3 mL) was stirred at 100 °C in an open reation vessel for ~ 4-10 hr (monitored by TLC) as listed in Table 1. The products were extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was then subjected to separation with flash column chromatography, using petroleum-distilled *n*-hexane/EtOAc (5:1) as an eluent, to give the corresponding pure products **6-11**.

Suzuki cross-coupling reactions of 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (3) with arylboronic acids in water-DMF using microwave irradiation. General procedure. A mixture of the above components and solvent were mixed thoroughly in a process glass vial. The vial was capped properly, and the mixture was heated

under microwave-irradiating conditions at 160 °C and 250 Watts for the appropriate reaction times as shown in Table 1. After the reaction was almost complete (by TLC), the products were extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered off, and the solvent was evaporated under reduced pressure. The residue was then subjected to separation with flash column chromatography, as described above, to give the corresponding pure cross-coupled products **6-11**.

3-(5-Phenylbenzofuran-2-yl)-1*H*-pyrazole (6). White crystals; mp 84-86 ºC; R_f 0.47 (hexane:ethyl acetate, 5:1); IR (KBr) υ 3375, 3139, 3036, 2922, 1600, 1442, 1256, 1072 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.76 (d, 1H, *J* 5.7 Hz, CH aromatic), 7.15 (s, 1H, CH aromatic), 7.26-7.47 (m, 3H, CH aromatic), 7.60 (d, 2H, *J* 7.8 Hz, CH aromatic), 7.69 (d, 1H, *J* 8.4 Hz, CH aromatic), 7.78 (d, 1H, *J* 8.1 Hz, CH aromatic), 7.88 (d, 1H, *J* 5.4 Hz, CH aromatic), 7.98 (s, 1H, CH aromatic), 13.81 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 101.1, 102.9, 110.9, 111.2, 120.8, 123.0, 123.3, 124.0, 126.8, 127.2, 128.5, 128.8, 129.9, 133.9, 153.8; MS *m/z* (%) 260 (5.9, M^+), 184 (100), 155 (33.1), 128 (40.7), 102 (55.9), 63 (74.6), 50 (83.1). Anal. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.55; H, 4.58; N, 10.69%.

3-(5-(*p*-Tolyl)benzofuran-2-yl)-1*H*-pyrazole (7). White crystals; mp 108-110 ºC; R_f 0.44 (hexane:ethyl acetate, 5:1); IR (KBr) υ 3356, 3139, 2921, 2846, 1614, 1442, 1348 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H, CH_3), 6.75 (d, 1H, *J* 6.9 Hz, CH aromatic), 7.13 (d, 2H, *J* 7.5 Hz, CH aromatic), 7.26 (d, 2H, *J* 7.5 Hz, CH aromatic), 7.58 (d, 1H, *J* 8.1 Hz, CH aromatic), 7.61 (s, 1H, CH aromatic), 7.69 (d, 1H, *J* 7.8 Hz, CH aromatic), 7.87 (d, 1H, *J* 6.9 Hz, CH aromatic), 7.88 (s, 1H, CH aromatic), 13.19 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.0, 101.1, 102.9, 110.9, 111.1, 112.9, 120.8, 123.0, 124.0, 126.6, 127.9, 129.4, 129.8, 134.1, 139.2, 153.8; MS *m/z* (%) 274 (100, M^+), 245 (10.6), 184 (16.8), 155 (23.5), 88 (15.1), 63 (23.5), 51 (18.4). Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.72; H, 5.22; N, 10.17%.

3-(5-(4-Methoxyphenyl)benzofuran-2-yl)-1*H*-pyrazole (8). Yellow crystals; mp 104-106 ºC; R_f 0.36 (hexane:ethyl acetate 5:1); IR (KBr) 3353, 3139, 2929, 2836, 1602, 1442, 1245, 1168 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.75 (s, 3H, OCH_3), 6.75 (d, 1H, *J* 6.3 Hz, CH aromatic), 6.88 (d, 2H, *J* 8.7 Hz, CH aromatic), 7.02 (d, 2H, *J* 9 Hz, CH aromatic), 7.59 (s, 1H, CH aromatic),7.61 (d, 1H, *J* 8.4 Hz, CH aromatic), 7.74 (d, 1H, *J* 8.4 Hz, CH aromatic), 7.81 (s, 1H, CH aromatic), 7.86 (d, 1H, *J* 6.3 Hz, CH aromatic), 13.19 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.1, 101.2, 102.9, 110.9, 111.1, 112.9, 114.2, 120.7, 120.9, 123.0, 124.1, 127.9, 128.5, 129.8, 135.7, 153.8; MS *m/z* (%) 290 (100, M^+), 275 (41.5), 247 (16.5), 189 (16.0), 145 (22.9), 87 (15.4), 55 (18.6). Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.33; H, 4.81; N, 9.58%.

3-(5-(4-Chlorophenyl)benzofuran-2-yl)-1*H*-pyrazole (9). White powder; mp 78-80 ºC; R_f 0.4 (hexane:ethyl acetate, 5:1); IR (KBr) υ 3379, 3141, 2925, 2844, 1590, 1442, 1257 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.75 (d, 1H, *J* 8.7 Hz, CH aromatic), 7.39 (d, 2H, *J* 8.1 Hz, CH aromatic), 7.51 (d, 1H, *J* 8.4 Hz, CH aromatic), 7.58 (s, 1H, CH aromatic), 7.72 (d, 1H, *J* 8.7 Hz, CH aromatic), 7.79 (d, 2H, *J* 8.1 Hz, CH aromatic), 7.86 (d, 1H, *J* 8.7 Hz, CH aromatic), 8.13 (s, 1H, CH aromatic), 13.22 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 102.9, 110.9, 111.3, 112.9, 120.7, 120.9, 123.0, 123.3, 127.3, 128.6, 128.7, 129.9, 135.8, 136.1, 153.8; MS *m/z* (%) 296 (33.3, M^++2), 295 (37.4, M^++1), 294 (100, M^+), 202 (29.3), 150 (12.2), 133 (24.4), 56 (15.4). Anal. Calcd for $C_{17}H_{11}ClN_2O$: C, 69.28; H, 3.76; N, 9.50. Found: C, 69.31; H, 3.77; N, 9.45%.

3-(5-(3,4-Methylenedioxophenyl)benzofuran-2-yl)-1*H*-pyrazole (10). Buff powder; mp 114-116 ºC; R_f 0.39 (hexane:ethyl acetate, 5:1); IR (KBr) υ 3427, 3139, 2921, 2845, 2361, 1437 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) υ 6.06 (s, 2H, OCH_2), 6.75 (d, 1H, *J* 6.6 Hz, CH aromatic), 6.88 (d, 1H, *J* 7.8 Hz, CH aromatic), 6.99 (d, 1H, *J* 7.8 Hz, CH aromatic), 7.16 (s, 1H, CH aromatic), 7.27 (s, 1H, CH aromatic), 7.60 (d, 1H, *J* 9 Hz, CH aromatic), 7.64 (d, 1H, *J* 8.7 Hz, CH aromatic), 7.84 (d, 1H, *J* 6.6 Hz, CH aromatic), 7.85 (s, 1H, CH aromatic), 13.29 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 101.1, 101.4, 102.9, 103.2, 107.3, 108.5, 110.9, 112.9, 115.4, 120.9, 123.0, 123.3,

124.1, 126.6, 128.4, 130.8, 152.6, 153.8; MS *m/z* (%) 304 (100, M^+), 264 (27.2), 184 (32.9), 128 (34.7), 92 (26.0), 51 (42.8). Anal. Calcd for $C_{18}H_{12}N_2O_3$: C, 71.05; H, 3.97; N, 9.21. Found: C, 70.92; H, 3.88; N, 9.15%.

3-(5-(Thien-3-yl)benzofuran-2-yl)-1*H*-pyrazole (11). Yellowish-white powder; mp 180-182 ºC; R_f 0.41 (hexane:ethyl acetate, 5:1); IR (KBr) υ 3439, 3135, 2916, 2361, 1436, 1044 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.76 (d, 1H, *J* 6.3 Hz, CH aromatic), 7.15 (s, 1H, CH aromatic), 7.22-7.44 (m, 2H, CH aromatic), 7.54 (s, 1H, CH aromatic), 7.59 (d, 1H, *J* 8.7 Hz, CH aromatic), 7.62 (d, 1H, *J* 9 Hz, CH aromatic), 7.86 (d, 1H, *J* 6.3 Hz, CH aromatic), 7.88 (s, 1H, CH aromatic), 13.25 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 100.7, 103.2, 110.9, 111.2, 112.9, 115.4, 120.2, 120.9, 123.3, 126.4, 126.6, 126.8, 129.9, 130.8, 152.6; MS *m/z* (%) 266 (16.2, M^+), 184 (17.6), 155 (25.7), 127 (46.3), 98 (27.9), 74 (66.9), 63 (88.2), 50 (100). Anal. Calcd for $C_{15}H_{10}N_2OS$: C, 67.65; H, 3.78; N, 10.52; S, 12.04. Found: C, 67.59; H, 3.82; N, 10.46; S, 11.97%.

Mizoroki-Heck cross-coupling reactions of 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (3) with olefins in DMF under thermal heating. A mixture of 3-(5-bromobenzofuran-2-yl)-*1H*-pyrazole (**3**) (263 mg, 1 mmol) and the appropriate olefin **12a-d** (1.5 mmol), TBAB (0.6 mmol), complex (**4**) (0.25 mol%), and TEA (303 mg, 3 mmol) in DMF (3 mL) was stirred at 130 °C in an open reaction vessel for 8h. After the reaction was almost complete (by TLC), the reaction mixture was left to cool to room temperature. The reaction mixture was then extracted three times with EtOAc (3 x 20 mL), and the organic fractions were combined, dried over $MgSO_4$, filtered, and the solvent was removed under vacuum. The residue was then subjected to purification via flash column chromatography with petroleum *n*-hexane/EtOAc (6:1) as eluent to give the corresponding pure products **13-16**.

Mizoroki-Heck cross-coupling reactions of 3-(5-bromobenzofuran-2-yl)-1*H*-pyrazole (3) with olefins in DMF under microwave heating. A mixture of 3-(5-bromobenzofuran-2-yl)-*1H*-pyrazole (**3**) (263 mg, 1 mmol) and the appropriate olefin **12a-d** (1.5 mmol), TBAB (0.6 mmol), complex (**4**) (0.25 mol%), and TEA (303 mg, 3 mmol) in DMF (3 mL) was mixed in a process glass vial. The vial was capped properly, and the mixture was heated under microwave-irradiating conditions at 160 °C and 250 Watt for 20 min. After the reaction was almost complete (by TLC), the reaction mixture was left to cool to room temperature. The reaction mixture was then extracted three times with EtOAc (3 x 20 mL), the organic fractions were combined, dried over $MgSO_4$, filtered and the solvent removed under vacuum. The residue was then subjected to purification via flash column chromatography with petroleum *n*-hexane/EtOAc (6:1) as eluent to give the corresponding pure products **13-16**.

(*E*)-3-(5-β-Styrylbenzofuran-2-yl)-1*H*-pyrazole (13). Pale yellow powder; mp 196-198 ºC; R_f 0.20 (hexane:ethyl acetate, 6:1); IR (KBr) υ 3376, 3140, 3021, 2917, 1448, 1254 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.76 (d, 1H, *J* 2.1 Hz, CH aromatic), 7.18 (s, 1H, CH aromatic), 7.24 (d, 1H, *J* 16.2 Hz, CH, olefinic), 7.28-7.38 (m, 3H, CH aromatic), 7.38 (d, 1H, *J* 15.9 Hz, CH, olefinic), 7.56-7.62 (m, 4H, CH aromatic), 7.86 (s, 2H, CH aromatic), 13.24 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 101.4, 103.0, 111.1, 118.7, 120.8, 120.9, 123.1, 126.2, 127.3, 127.4, 127.8, 128.2, 128.6, 129.0, 132.5, 137.1, 153.6; MS *m/z* (%) 286 (100, M^+), 257 (14.6), 227 (17.4), 189 (30.6), 163 (17.4), 129 (17.4), 95 (37.5), 63 (25.0). Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.76; H, 4.85; N, 9.68%.

(*E*)-3-(2-(1*H*-Pyrazol-3-yl)benzofuran-5-yl)acrylonitrile (14). Buff powder; mp 154-156 ºC; R_f 0.24 (hexane:ethyl acetate, 6:1); IR (KBr) υ 3273, 3141, 3043, 2935, 2842, 2211, 1619, 1450, 1268 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.44 (d, 1H, *J* 16.5 Hz, CH, olefinic), 6.77 (s, 1H, CH aromatic), 7.20 (s, 1H, CH aromatic), 7.62 (d, 1H, *J* 9 Hz, CH aromatic), 7.68 (d, 1H, *J* 8.4 Hz, CH aromatic), 7.75 (d, 1H, *J* 16.8 Hz, CH olefinic), 7.89 (s, 1H, CH aromatic), 7.93 (s, 1H, CH aromatic), 13.24 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 95.2, 101.2, 103.1, 111.6, 118.9, 120.7, 120.8, 120.9, 121.6, 123.8, 129.2, 129.9, 150.8, 155.2; MS *m/z* (%) 235 (100, M^+),

179 (19.1), 151 (19.1), 128 (31.9), 76 (57.4), 62 (44.7), 50 (29.8). Anal. Calcd for $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86. Found: C, 71.41; H, 3.80; N, 17.83%.

(*E*)-Ethyl 3-(2-(1*H*-pyrazol-3-yl)benzofuran-5-yl)acrylate (15). White crystals; mp 180-182 ºC; R_f 0.14 (hexane:ethyl acetate 7:1); IR (KBr) υ 3238, 3115, 3062, 2986, 1682, 1367, 1294, 1237, 1038 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, 3H, *CH3*CH2-, *J* 7.2 Hz), 4.20 (q, 2H, CH3*CH2-*, *J* 7.2 Hz), 6.62 (d, 1H, *J* 16.2 Hz, CH olefinic), 6.77 (s, 1H, CH aromatic), 7.17 (s, 1H, CH aromatic), 7.64 (d, 1H, *J* 8.4 Hz, CH aromatic), 7.69 (d, 1H, *J* 9 Hz, CH aromatic), 7.76 (d, 1H, *J* 15.9 Hz, CH, olefinic), 7.88 (s, 1H, CH aromatic), 8.00 (s, 1H, CH aromatic), 13.22 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.1, 59.8, 101.2, 103.1, 111.5, 116.8, 121.4, 124.5, 129.1, 129.4, 129.9, 141.9, 144.7, 152.5, 154.9, 166.2; MS *m/z* (%) 282 (100, M^+), 237 (61.2), 210 (26.0), 152 (15.3), 77 (18.0), 63 (27.3). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.11; H, 4.95; N, 9.89%.

(*E*)-Butyl 3-(2-(1*H*-pyrazol-3-yl)benzofuran-5-yl)acrylate (16). White powder; mp 146-148 ºC; R_f 0.26 (hexane:ethyl acetate 6:1); IR (KBr) υ 3423, 3142, 3043, 2954, 2864, 1709, 1631, 1447, 1260, 1170 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.92 (t, 3H, *J* 7.5 Hz, $CH_3CH_2CH_2CH_2$), 1.35-1.43 (m, 2H, $CH_3CH_2CH_2CH_2$), 1.59-1.66 (m, 2H, $CH_3CH_2CH_2CH_2$), 4.16 (t, 2H, *J* 6.6 Hz, $CH_3CH_2CH_2CH_2$), 6.62 (d, 1H, *J* 15.9 Hz, CH, olefinic), 6.77 (d, 1H, *J* = 2.1 Hz, CH aromatic), 7.18 (s, 1H, CH aromatic), 7.64 (d, 1H, *J* 8.7 Hz, CH aromatic), 7.70 (d, 1H, *J* 9 Hz, CH aromatic), 7.76 (d, 1H, *J* 15.9 Hz, CH olefinic), 7.88 (s, 1H, CH aromatic), 8.00 (s, 1H, CH aromatic), 13.24 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.5, 18.6, 30.2, 63.5, 101.2, 103.1, 111.4, 116.8, 121.5, 124.5, 129.2, 129.4, 130.0, 141.9, 144.7, 152.5, 154.9, 166.3; MS *m/z* (%) 310 (89.5, M^+), 254 (100), 237 (75.3), 210 (26.0), 154 (14.2), 105 (25.3), 63 (31.8). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.54; H, 5.77; N, 8.93%.

Supplementary Materials

Copies of ^1H and ^{13}C spectra for compounds **2**, **3**, **6**-**11**, and **13**-**16** associated with this article can be found in the online version of the text.

References

1. Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270–5298. https://doi.org/10.1039/c3cs35521g
2. Bonin, H.; Fouquet, E.; Felpin, F. X. *Adv. Synth. Catal.* **2011**, *353*, 3063–3084. https://doi.org/10.1002/adsc.201100531
3. Knappke, C. E. I.; Von Wangelin, A. J. *Angew. Chemie - Int. Ed.* **2010**, *49*, 3568–3570. https://doi.org/10.1002/anie.201001028
4. Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047–3101. https://doi.org/10.1016/j.tet.2007.12.036
5. Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83–90. https://doi.org/10.1016/S0022-328X(02)01269-X
6. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. https://doi.org/10.1021/cr00039a007
7. Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31–44.

https://doi.org/10.1039/B611547K

8. Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771–11835. https://doi.org/10.1016/j.tet.2005.08.054
9. Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2964. https://doi.org/10.1021/cr020039h
10. Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146–151. https://doi.org/10.1021/ar50136a006
11. Gawande, M. B.; Shelke, S. N.; Zboril, R.; Varma, R. S. *Acc. Chem. Res.* **2014**, *47*, 1338–1348. https://doi.org/10.1021/ar400309b
12. Kappe, C. O.; Stadler, A. Microwave Theory. In *Microwaves in Organic and Medicinal Chemistry*; Wiley-Blackwell, 2005; pp. 9–28. https://doi.org/10.1002/3527606556
13. de la Hoz, A.; Díaz-Ortiz, Á.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164–178. https://doi.org/10.1039/B411438H
14. Tierney, J. P.; Lidstrom, P. *Microwave Assisted Organic Synthesis*; Blackwell: Oxford, 2005. https://doi.org/10.1002/9781444305548
15. Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. *Chem. Rev.* **2018**, *118*, 679–746. https://doi.org/10.1021/acs.chemrev.7b00417
16. Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725–748. https://doi.org/10.1021/cr800448q
17. Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997.
18. Aslam, S. N.; Stevenson, P. C.; Phythian, S. J.; Veitch, N. C.; Hall, D. R. *Tetrahedron* **2006**, *62*, 4214–4226. https://doi.org/10.1016/j.tet.2006.02.015
19. de Campos, M. P.; Filho, V. C.; da Silva, R. Z.; Yunes, R. A.; Zaccino, S.; Juarez, S.; Bella Cruz, R. C.; Bella Cruz, A. *Biol. Pharm. Bull.* **2005**, *28*, 1527–1530. https://doi.org/10.1248/bpb.28.1527
20. Carlsson, B.; Singh, B.N.; Temciuc, M.; Nilsson, S.; Li, Y.; Mellin, C.; Malm, J. *J. Med. Chem.* **2002**, *45*, 623–630. https://doi.org/10.1021/jm001126+
21. Spaniol, M.; Bracher, R.; Ha, H. R.; Follath, F.; Kralhenbühl, S. *J. Hepatol.* **2001**, *35*, 628–636. https://doi.org/10.1016/S0168-8278(01)00189-1
22. Narimatsu, S.; Takemi, C.; Kuramoto, S.; Tsuzuki, D.; Hichiya, H.; Tamagake, K.; Yamamoto, S. *Chirality* **2003**, *15*, 333-339. https://doi.org/10.1002/chir.10212
23. Dawood, K. M. *Expert Opin. Ther. Pat.* **2013**, *23*, 1133–1156. https://doi.org/10.1016/j.tet.2006.02.015
24. Dawood, K. M.; Abdel-Gawad, H.; Ellithey, M.; Mohamed, H. A.; Hegazi, B. *Arch. Pharm. Chem. Life Sci.* **2006***, 339,* 133 –140. https://doi.org/10.1002/ardp.200500176
25. Dawood, K. M.; Abdel-Gawad, H.; Rageb, E. R.; Ellithey, M.; Mohamed, H. A. *Bioorg. Med. Chem.* **2006**, *14*, 3672-3680. https://doi.org/10.1016/j.bmc.2006.01.033
26. Abdel-Aziz, H. A.; Mekawey, A. A. I.; Dawood, K. M. *Eur. J. Med. Chem.* **2009**, *44*, 3637–3644.

https://doi.org/10.1016/j.ejmech.2009.02.020

27. Yar, M. S.; Abdullah, M. M.; Husain, A; Bhakht, M. A.; De Clercq, E. *J. Enzyme Inhib. Med. Chem.* **2009***, 24,* 949-956. https://doi.org/10.1080/14756360802560677
28. Coskun, D.; Ahmedzade, M.; Kirbag, S. *E-J. Chem.* **2011**, *8*, 1574–1581. https://doi.org/10.1155/2011/806854
29. Manna, K.; Agrawal, Y. K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2688–2692. https://doi.org/10.1016/j.bmcl.2009.03.161
30. Suthakaran, R.; Somasekhar, G.; Sridevi, C.; Marikannan, M.; Suganthi, K.; Nngarajan, G. *Asian J. Chem***. 2007**, *19*, 3353-3362.
31. Babu, V. H.; Sridevi, C.; Joseph, A.; Srinivasan, K. K. *Indian J. Pharm. Sci.* **2007**, *69*, 470-473. https://doi.org/10.4103/0250-474X.34569
32. Jackson, Y. A.; Williams, M. F.; Williams, L. A. D.; Morgan, K. K.; Redway, F. A. *Pesticide Sci.***1998***, 53*, 241-244. https://doi.org/10.1002/(SICI)1096-9063(199807)53:3<241::AID-PS763>3.0.CO;2-F
33. Dawood, K. M.; Kirschning, A. *Tetrahedron* **2005**, *61*, 12121. https://doi.org/10.1016/j.tet.2005.07.113
34. Dawood, K. M. *Tetrahedron* **2007**, *63,* 9642; https://doi.org/10.1016/j.tet.2007.07.029
35. Dawood, K. M.; Solodenko, W.; Kirschning, A. *Arkivoc* **2007** *(v*), 104. http://dx.doi.org/10.3998/ark.5550190.0008.510
36. Dawood, K. M.; Fayed, M. S.; Elkhalea, M. M. *Arkivoc* **2009** (*xiii*), 324. http://dx.doi.org/10.3998/ark.5550190.0010.d28
37. Dawood, K. M.; Eldeftar, M. M. *Synthesis* **2010**, 1030-1038. https://doi.org/10.1055/s-0029-1218662
38. Darweesh, A. F.; Shaaban, M. R.; Farag, A. F.; Metz, P.; Dawood, K. M. *Synthesis* **2010**, 3163-3173.
39. Shaaban, M. R.; Darweesh, A. F.; Dawood, K. M.; Farag, A. F. *Arkivoc* **2010** (*x*), 208-225. http://dx.doi.org/10.3998/ark.5550190.0011.a18
40. Dawood, K. M.; Farag, A. M.; El-Deftar, M. M.; Gardiner, M.; Abdelaziz, H. A. *Arkivoc* **2013** *(iii*), 210-226. http://dx.doi.org/10.3998/ark.5550190.0014.317
41. Dawood, K. M.; Elamin, M. B.; Farag, A. M.; Farag, *Arkivoc* **2015**, (*vii*), 50-62 http://dx.doi.org/10.3998/ark.5550190.p009.018
42. Hassaneen, H. M.; Dawood, K. M.; Ahmed, M. S. M.; Abdelhadi, H. Y.; Mohamed, M. A.-M. *Arkivoc* **2015**, (*v*), 334-349. http://dx.doi.org/10.3998/ark.5550190.p009.123
43. Dawood, K. M.; Elamin, M. B.; Farag, A. M. *J. Heterocycl. Chem*. **2016**, *53*, 1928–1934. https://doi.org/10.1002/jhet.2508
44. Dawood, K. M.; Shaaban, M. R.; Elamin, M. B.; Farag, A. M. *Arab. J. Chem.* **2017**, *10*, 473-479. https://doi.org/10.1016/j.arabjc.2013.06.004
45. Paizs, C.; Toşa, M.; Majdik, C.; et al.. *Tetrahedron Asymm.* **2003**, *14*, 1495–1501. https://doi.org/10.1016/S0957-4166(03)00222-2
46. A. O. Abdelhamid, A. A. Fahmi, and B. S. Baaiu, *J. Heterocyclic Chem.* **2016**, *53*, 1917-1927.

