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Pd-catalyzed cross-coupling reactions of benzo- and thieno-annelated pyrimidinones, possessing the benzylsulfanyl moiety

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3-Benzyl-2-(benzylsulfanyl)quinazolin-4(3*H*)-one and 3-benzyl-2-(benzylsulfanyl)[1]-benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one bearing the benzylsulfanyl group as a leaving partner were engaged in copper-mediated palladium-catalyzed cross-coupling reactions with a range of (hetero)aromatic boronic acids and the corresponding organotin derivatives. These results could extend the scope and library of new condensed polyheteroaromatic systems chemistry.

Key words: cross-coupling, Stille reaction, Suzuki reaction, pyrimidinone

INTRODUCTION

Metal-catalyzed coupling reactions have developed the most powerful tools for synthetic chemists over the past two decades [1]. Palladium-catalyzed cross-coupling has achieved high success in the construction and functionalization of heteroaromatic series at all scales of production: from preparation of the fine chemicals and pharmaceuticals to bulk industrial chemicals. An importance of palladium chemistry is evident from the tremendous amount of publications in regard to this domain, especially for heterocycles [2–6]. Furthermore, palladium is usually used in catalytic amounts and catalyzes unique chemical transformations, which cannot be achieved using classical techniques. The great advantage is the mildness of the conditions of these transformations and the tolerance of many functional groups. Most palladium-catalyzed reactions proceeded stereo and with regioselectivity in excellent yields [7]. The cross-coupling reactions, representing one of the most powerful tools for a new C–C bond construction in modern chemistry, have brought palladium to the forefront [8, 9]. For this aim, today Stille and Suzuki reactions rank among the most general transformations in organic synthesis. Classically, the Stille reaction involves the cross-coupling between organostannanes and aryl or alkenyl halides, pseudo halides, triflates or arenediazonium salts [5, 10]. The Suzuki reaction involves the cross-coupling of organoboron reagents with aryl, alkyl, alkenylhalides or triflates, usually in the presence of a base [2].

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Liebeskind and co-workers developed a new efficient palladium-catalyzed cross-coupling methodology involving thiol ester and thioether type species [11–13]. Thiols or thioethers are acting as leaving groups in modified Stille, Suzuki and Sonogashira coupling reactions. These modified conditions require Pd(0)-catalyst and the stoichiometric amount of copper(I)-promoter under neutral conditions for efficient coupling with boronic acids or organostannanes. As a metal cofactor, copper(I) bromide dimethyl sulfide complex (CuBr Me_2S) either copper(I) thiophene-2-carboxylate (CuTC) or copper(I) 3-methylsalicylate (CuMeSal) are generally used [14–18].

On the other hand, the pyrimidinones ring system is an important skeleton in biologically active compounds due to their diverse pharmacological properties as antibacterial [19], anti-inflammatory, analgesic [20], antitumor [21], antiproliferative [22], and anti-HIV-1 agents [23]. Their synthesis has been in focus of considerable attention in the synthetic organic chemistry as well as in the medicinal chemistry. Recently, pyrrolo[2,3-*d*]pyrimidin-4-ones were synthesized as new potential corticotropin-releasing factor 1 (CRF1) receptor antagonists with a carbonyl-based hydrogen bonding acceptor [24]. Benzothienopyrimidinones were discovered as a novel class of Pim inhibitors that simultaneously inhibit all three Pim kinases [25].

Considering a great importance of pyrimidinones, in this paper we present new results of palladium-catalyzed modified Stille and Suzuki coupling reactions between organostannanes or organoboranes and benzo- and thieno-annelated pyrimidinones **1** and **2**, respectively, bearing benzylthioether as a leaving group.

RESULTS AND DISCUSSION

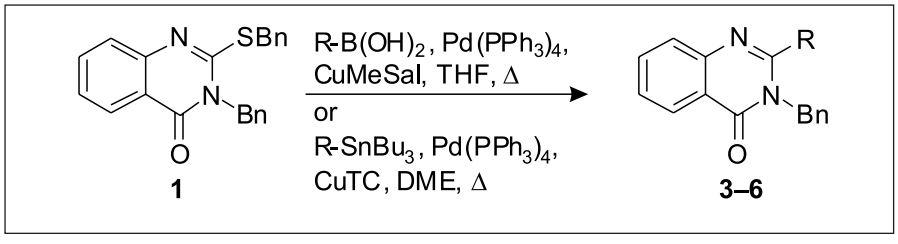
The precursors 3-benzyl-2-(benzylsulfanyl)quinazolin 4(3*H*)-one **1** and 3-benzyl-2-(benzylsulfanyl)[1]benzothieno[3,2-*d*] pyrimidin-4(3*H*)-one **2** were prepared from methyl 2-isothiocyanatobenzoate and methyl 3-isothiocyanato-2,3 -dihydro-1-benzothiophene-2-carboxylate, respectively, by a smooth cyclization in a toluene-pyridine mixture [26]. Then the corresponding 3-benzyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one and 3-benzyl-2-thioxo-2,3-dihydro[1] benzothieno[3,2-*d*]pyrimidin-4(1*H*)-one were selectively *S*-benzylated using standard conditions to afford the respective 2-benzylsulfanylderivatives **1** and **2**, which were used as starting materials in copper-assisted palladium-catalyzed cross-coupling reactions [26].

Firstly, the Stille coupling of quinazolinone derivative **1**, as a model system, was investigated. 4- and 3-(tri-*n*-butyltin) pyridines were chosen as coupling reagents due to the importance of the pyridine ring in the synthesis of potentially biologically active compounds (Scheme 1).

In accordance with literature [15, 17], the Stille reaction depends on several factors: the type of the substrate, the polarity of the solvent, the type and concentration of the palladium(0) catalyst, the type and excess of the copper(I) salt as well as the organotin derivatives and finally – on the reaction time. In our case, longer reaction times were needed for the synthesis of pyrimidin-4-ones in good yields. For example, when 4-(tri-*n*-butylstannyl)pyridine was used as a coupling reagent, the yield of the coupled product **4** after 5 h of refluxing was only 8%, while prolonging the reaction to 64 h increased the yield to 63%. The reactions were followed by TLC and stopped when the formation of the product did not seem to go up. It was determined that the most appropriate solvent in Stille reactions of quinazolinone derivative **1** is dimethoxyethane (DME) [14].

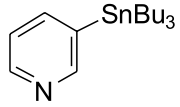
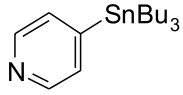
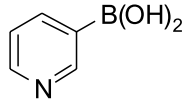
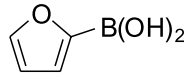
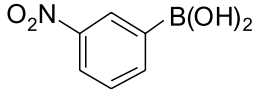
The modified Stille coupling of 3-benzyl-2-(benzylsulfanyl)quinazolin-4(3*H*)-one **1** with 4-(tri-*n*-butylstannyl) pyridine and 3-(tri-*n*-butylstannyl)pyridine was investigated under standard Liebeskind-Srogl palladium-catalyzed reaction conditions [12]. As a metal cofactor, CuTC was used, which is especially effective for substrates that are not stable at elevated temperatures. Refluxing of a solution of quinazolinone **1** with 2.2 equiv of organotin derivatives, 5 mol% of $Pd(PPh_3)_4$, and 2.2 equiv of CuTC in DME for 48 h under inert (argon) atmosphere gave the desired coupling compounds **3** and **4** in 41% and 44% isolated yields, respectively. Notwithstanding these mediocre results for the Stille coupling, we were keen to apply the modified conditions for the Suzuki reaction. Extension of the reactions with different organostannanes and boronic acids under the modified coupling conditions gave the results summarized in Table 1.

As an alternative to Stille, Suzuki reactions were investigated with 3-pyridine-, 2-furan- and 3-nitrophenylboronic acids and 3-benzyl-2-(benzylsulfanyl)quinazolin-4(3*H*)-one **1**. In this case, CuMeSal was used as a metal cofactor (Scheme 1). The reactions proceeded more effectively while refluxing 1 equiv of quinazolinone derivative **1**, 2.2 equiv of boronic



Scheme 1

Table 1. **Conditions of Stille and Suzuki reactions on quinazolinone derivative 1**

Entry	Coupling reagent	Time	Product	Yield
1		45 h	**3**	41%
2		64 h	**4**	46%
3		46 h	**3**	76%
4		48 h	**5**	62%
5		48 h	**6**	75%

acids, 2.2 equiv of CuMeSal, and 10 mol% of $Pd(PPh_3)_4$ in THF under inert (argon) atmosphere [13, 14, 17, 27]. After 48 h of refluxing, we were delighted to afford efficient results – the compounds **3**, **5** and **6** were isolated in good yields ranging from 62% to 76% (entries 3–5, Table 1). From a small selection of the reagents chosen, it could be seen that both 3-pyridine- and 3-nitrophenylboronic acids gave the best results (entries 3 and 5, Table 1).

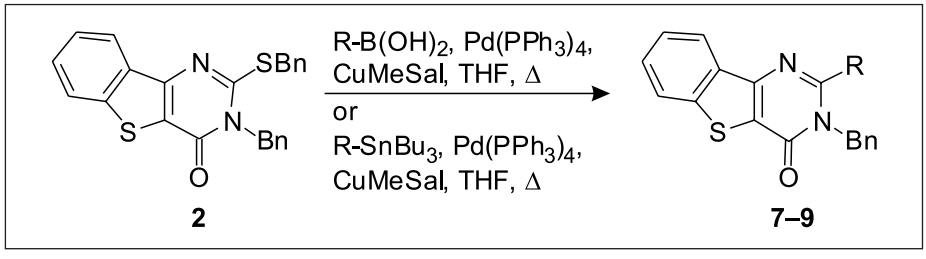
Finally, the same Stille and Suzuki coupling reactions conditions were applied for 3-benzyl-2-(benzylsulfanyl)[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one **2** with boronic acids and organotin derivatives to obtain C–C coupled compounds **7**–**9**.

Like previously, benzothienopyrimidinone **2** was coupled with several organotin derivatives (3- and 4-(tri-*n*-butyltin) pyridines and 2-(tributylstannanyl)furan) under the similar Stille reaction conditions using CuMeSal as a metal cofactor (Scheme 2). The investigation of reactions on benzothienopyrimidinone derivative **2** with 3- and 4-(tri-*n*-butyltin) pyridines has not given the desired compounds. The reactions mixtures were inseparable by flash chromatography. Using 2-(tributylstannanyl)furan as a coupling reagent gave the Stille coupling product **7** in moderate yield (entry 1, Table 2).

Further, the reactivity of 3-benzyl-2-(benzylsulfanyl)[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one **2** was investigated using the similar modified Suzuki coupling conditions than with quinazolinone derivative **1**. Benzothieno[3,2-*d*]pyrimidin-4-one **2** was investigated with 3-pyridine-2-furan- and 3-nitrophenylboronic acids but the reactions revealed to be more sluggish. 3-benzyl-2-(benzylsulfanyl)[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one **2** with 3-pyridine- and 2-furylboronic acids showed moderate reactivity, leading to the cross-coupled products **7** and **8** in 46% and 44% yields, respectively (entries 2 and 3, Table 2). However, the coupling with 3-nitrophenylboronic acid is promising as the isolated yield was higher (entry 4, Table 2).

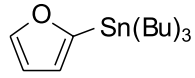
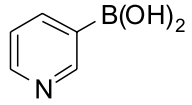
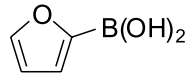
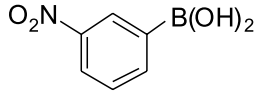
EXPERIMENTAL

Melting points (mp) were determined on a Büchi 510 apparatus and are uncorrected. IR spectra (KBr disk or film on NaCl disk) were recorded on Thermo Nicolet 6700 or Perkin-Elmer Paragon 1000 PC spectrophotometers, frequencies being given in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance DPX-250 instrument (250 MHz ^1H frequency / 62.5 MHz ^{13}C frequency). Chemical shifts (δ) are



Scheme 2

Table 2. **Conditions of Stille and Suzuki reactions on benzothienopyrimidinone derivative 2**

Entry	Coupling reagent	Time	Product	Yield
1		46 h	**7**	40%
2		48 h	**8**	44%
3		45 h	**7**	46%
4		46 h	**9**	54%

reported in ppm from an internal TMS standard. Whenever appropriate, signal assignments were deduced from DEPT, COSY and CH CORRELATION NMR experiments. Mass measurements were carried out using the Ion Spray® (IS) method with an API 300 Perkin-Elmer SCIEX spectrometer. Elemental analysis was performed with an Exeter Analytical CE-440 Elemental Analyzer. Analytical TLC was carried out on Silica Gel 60F-254 plates (E. Merck); spots were visualized by UV light (254 nm) and developed by charring after spraying a $KMnO_4$ solution. Column chromatography was carried out on Silica Gel SI 60 (43–60 μm) (E. Merck) using mixtures of petroleum ether (PE) and ethyl acetate (EA).

3-Benzyl-2-(pyridin-3-yl)quinazolin-4(3*H*)-one (3)

Method A. To a solution of compound **1** (0.062 g, 0.173 mmol) in dry 1,2-dimethoxyethane (10 ml), copper thiophene 2-carboxylate (0.073 g, 0.380 mmol) and 3-(tributilstannyl)pyridine (0.140 g, 0.380 mmol) were added. After stirring at room temperature for 10 min, tetrakis(triphenylphosphine) palladium (0.010 g, 0.009 mmol) was added, then the suspension was refluxed for 43 h. The reaction mixture was diluted with dichloromethane and washed with saturated Na_2CO_3 aqueous solution and brine, and finally dried over $MgSO_4$. After filtration, the solvent was removed by evaporation in *vacuo*. The obtained residue was purified by flash chromatography (eluent: PE/EA: 2/8) to afford compound **3** (0.022 g, 41%) as a brown solid.

Method B. To a solution of compound **1** (0.100 g, 0.279 mmol) in dry THF (10 ml), copper 3-methylsalicylate (0.132 g, 0.614 mmol) and 3-pyridineboronic acid (0.075 g, 0.614 mmol) were added. After stirring at room temperature for 10 min, tetrakis(triphenylphosphine) palladium (0.032 g, 0.028 mmol) was added, then the suspension was refluxed for 46 h. The reaction mixture was diluted with dichloromethane and washed with saturated Na_2CO_3 aqueous solution and brine, and finally dried over $MgSO_4$. After filtration, the solvent was removed by evaporation in *vacuo*. The obtained residue was purified by flash chromatography (eluent: PE/EA: 2/8) to afford compound **3** (0.066 g, 76%) as a brown solid. M. p. 124 °C. IR (KBr): 1675 (C = O), 1595, 1563, 1474, 1376, 1157, 1026, 785, 712, 697 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6), δ: 5.20 (s, 2H, CH_2), 6.91 (s, 2H, CH_{Ar}), 7.21 (s, 3H, CH_{Ar}), 7.51–7.66 (m, 2H, CH_{Ar}, $CH_{pyridyl}$), 7.75 (d, 1H, ^3J = 7.5 Hz, H-8), 7.87–7.90 (m, 2H, CH_{Ar}, $CH_{pyridyl}$), 8.25 (d, 1H, ^3J = 7.5 Hz, H-5), 8.81 (br s, 2H, $CH_{pyridyl}$). ^{13}C NMR (62.5 MHz, DMSO-d_6), δ: 48.0 (CH_2), 120.3, 126.1 (2 × CH), 126.4, 127.1, 127.3, 127.5, 128.4 (2 × CH), 131.3, 131.4, 134.7, 135.4, 136.4, 146.7, 148.2, 150.3, 153.8 (C = O), 161.2 (N–C = N). MS (IS), *m/z*: 314.5 $[M + H]^+$. Anal. calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.40; H, 4.57; N, 13.23.

3-Benzyl-2-(pyridin-4-yl)quinazolin-4(3*H*)-one (4)

To a solution of compound **1** (0.100 g, 0.279 mmol) in dry DME (10 ml), copper thiophene carboxylate (0.117 g, 0.614 mmol) and 4-(tributilstannyl)pyridine (0.226 g, 0.614 mmol) were added. After stirring at room temperature for 10 min, tetrakis(triphenylphosphine) palladium (0.016 g, 0.014 mmol) was added, then the suspension was refluxed for 64 h. The reaction mixture was diluted with dichloromethane and washed with saturated Na_2CO_3 aqueous solution and brine, and finally dried over $MgSO_4$. After filtration, the solvent was removed by evaporation in *vacuo*. The obtained residue was purified by flash chromatography (eluent: PE/EA: 2/8) to afford compound **4** (0.040 g, 46%) as a yellow amorphous solid. IR (KBr): 1679 (C = O), 1591, 1569, 1468, 1370, 1152, 1024, 780, 715 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6), δ: 5.16 (s, 2H, CH_2), 6.90–6.93 (m, 2H, CH_{Ar}), 7.20–7.23 (m, 3H, CH_{Ar}), 7.44–7.67 (m, 4H, CH_{Ar}, $CH_{pyridyl}$), 7.91 (t, 1H, ^3J = 7.5 Hz, H-7), 8.24 (d, 1H, ^3J = 7.5 Hz, H-5), 8.65 (br s, 2H, $CH_{pyridyl}$). ^{13}C NMR (62.5 MHz, DMSO-d_6), δ: 48.1 (CH_2), 120.2, 126.1 (2 × CH), 126.4, 127.0 (2 × CH), 127.2, 127.4, 128.4 (2 × CH), 130.1 (2 × CH), 134.7, 136.6, 146.8, 148.6, 150.3, 154.0 (C = O), 161.0 (N–C = N). MS (IS), *m/z*: 314.5 $[M + H]^+$. Anal. calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.24; H, 4.71; N, 13.22.

3-Benzyl-2-(furan-2-yl)quinazolin-4(3*H*)-one (5)

To a solution of compound **1** (0.100 g, 0.279 mmol) in dry THF (10 ml), copper 3-methylsalicylate (0.132 g, 0.614 mmol) and 2-furylboronic acid (0.102 g, 0.614 mmol) were added. After stirring at room temperature for 10 min, tetrakis(triphenylphosphine) palladium (0.032 g, 0.028 mmol) was added, then the suspension was refluxed for 48 h. The reaction mixture was diluted with dichloromethane and washed with saturated Na_2CO_3 aqueous solution and brine, and finally dried over $MgSO_4$. After filtration, the solvent was removed by evaporation in *vacuo*. The obtained residue was purified by flash chromatography (eluent: PE/EA: 6/4) to afford compound **5** (0.074 g, 75%) as a yellow solid. M. p. 108–109 °C. IR (KBr): 1669 (C = O), 1587, 1515, 1470, 1378, 1160, 1027, 767, 715, 698 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$), δ: 5.60 (s, 2H, CH_2), 6.49 (dd, 1H, ^3J = 1.7 Hz, ^3J = 3.5 Hz, furyl), 6.90 (d, 1H, ^3J = 3.5 Hz, CH_{furyl}), 7.10–7.53 (m, 4H, CH_{Ar}, CH_{furyl}), 7.57 (d, 1H, ^3J = 1.7 Hz, CH_{furyl}), 7.76–7.78 (m, 2H, CH_{Ar}), 8.33 (d, 1H, ^3J = 7.7 Hz, H-5). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ: 48.0 (CH_2), 111.8, 115.4, 120.6, 126.5, 127.1, 127.2, 127.4, 127.6, 128.4, 128.6, 129.8, 134.5 136.6, 144.4, 146.3, 147.2, 147.3 (C = O), 162.3 (N–C = N). MS (IS), *m/z*: 303.5 $[M + H]^+$. Anal. calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.05; H, 4.52; N, 9.09.

3-Benzyl-2-(3-nitrophenyl)quinazolin-4(3*H*)-one (6)

To a solution of compound **1** (0.100 g, 0.279 mmol) in dry THF (10 ml), copper 3-methylsalicylate (0.132 g, 0.614 mmol) and 3-nitrophenylboronic acid (0.102 g, 0.614 mmol) were added. After stirring at room temperature for 10 min, tetrakis(triphenylphosphine) palladium (0.032 g, 0.028 mmol) was added, then the suspension was refluxed for 48 h. The reaction mixture was diluted with dichloromethane and washed with saturated Na_2CO_3 aqueous solution and brine, and finally dried over $MgSO_4$. After filtration, the solvent was removed by evaporation in *vacuo*. The obtained residue was purified by flash chromatography (eluent: PE/EA: 6/4) to afford compound **6** (0.074 g, 75%) as a yellow solid. M. p. 56–57 °C. IR (KBr): 1672 (C = O), 1549 (Ar-NO_2), 1475, 1353 (Ar-NO_2), 1154, 779, 719, 701 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6), δ: 5.26 (s, 2H, CH_2), 6.86–6.88 (m, 2H, CH_{Ar}), 7.20–7.85 (m, 8H, CH_{Ar}), 8.16 (s, 1H, CH_{Ar}), 8.31 (d, 1H, ^3J = 8.0 Hz, CH_{Ar}), 8.40 (d, 1H, ^3J = 7.7 Hz, H-5). ^{13}C NMR (62.5 MHz, DMSO-d_6), δ: 48.6 (CH_2), 120.8, 123.5, 124.5, 126.5 (2 × CH), 127.2, 127.6, 127.8, 128.3 (2 × CH), 128.8, 129.6, 133.7, 134.8, 136.0, 136.6, 146.8, 147.8, 153.8 (C = O), 162.1 (N–C = N). MS (IS), *m/z*: 358.5 $[M + H]^+$. Anal. calcd for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.18; H, 4.44; N, 11.59.

3-Benzyl-2-(furan-2-yl)[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (7)

Method A. To a solution of compound **2** (0.090 g, 0.217 mmol) in dry THF (10 ml), copper 3-methylsalicylate (0.103 g, 0.478 mmol) and 2-(tributylstannanyl)furan (0.150 g, 0.478 mmol) were added. After stirring at room temperature for 10 min, tetrakis(triphenylphosphine) palladium (0.013 g, 0.011 mmol) was added, then the suspension was refluxed for 43 h. The reaction mixture was diluted with dichloromethane and washed with saturated Na_2CO_3 aqueous solution and brine, and finally dried over $MgSO_4$. After filtration, the solvent was removed in *vacuo*. The obtained residue was purified by flash chromatography (eluent: PE/EA: 8/2) to afford compound **7** (0.031 g, 40%) as a yellow solid.

Method B. To a solution of compound **2** (0.090 g, 0.217 mmol) in dry THF (10 ml), copper 3-methylsalicylate (0.103 g, 0.478 mmol) and 2-furylboronic acid (0.054 g, 0.478 mmol) were added. After stirring at room temperature for 10 min, tetrakis(triphenylphosphine) palladium (0.013 g, 0.011 mmol) was added, then the suspension was refluxed for 46 h. The reaction mixture was diluted with dichloromethane and washed with saturated Na_2CO_3 aqueous solution and brine, and finally dried over $MgSO_4$. After filtration, the solvent was removed by evaporation in *vacuo*. The obtained residue was purified by flash chromatography (eluent: PE/EA: 8/2) to afford compound **7** (0.036 g, 46%) as a yellow solid. M. p. 194–195 °C. IR (KBr): 1673 (C=O), 1528, 1501, 1425, 1168, 1025, 945, 766, 754, 718, 696 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6), δ: 5.64 (s, 2H, CH_2), 6.71 (dd, 1H, ^3J = 1.8 Hz, ^3J = 3.5 Hz, CH_{furyl}), 7.11–7.18 (m, 3H, CH_{Ar}), 7.23–7.30 (m, 3H, CH_{Ar}, CH_{furyl}), 7.61–7.96 (m, 2H, CH_{Ar}, CH_{furyl}), 8.20 (d, 1H, ^3J = 7.7 Hz, H-8), 8.31 (d, 1H, ^3J = 7.7 Hz, H-5). ^{13}C NMR (62.5 MHz, DMSO-d_6), δ: 47.6 (CH_2), 112.2, 116.3, 121.2, 123.4 (2 × CH), 124.0, 125.7, 126.0 (2 × CH), 127.1, 128.6, 129.5, 133.8, 136.6, 140.8, 145.9, 146.3, 148.2, 151.4 (C = O), 158.1 (N–C = N). MS (IS), *m/z*: 359.5 $[M + H]^+$. Anal. calcd for $C_{21}H_{14}N_2O_2S$: C, 70.37; H, 3.94; N, 7.82. Found: C, 70.03; H, 3.89; N, 7.71.

3-Benzyl-2-(pyridin-3-yl)[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (8)

To a solution of compound **2** (0.100 g, 0.241 mmol) in dry THF (10 ml), copper 3-methylsalicylate (0.114 g, 0.531 mmol) and 3-pyridinylboronic acid (0.065 g, 0.531 mmol) were added. After stirring at room temperature for 10 min, tetrakis(triphenylphosphine) palladium (0.014 g, 0.012 mmol) was added, then the suspension was refluxed for 48 h. The reaction mixture was diluted with dichloromethane and washed with saturated Na_2CO_3 aqueous solution and brine, and finally dried over $MgSO_4$. After filtration, the solvent was removed by evaporation in *vacuo*. The obtained residue was purified by flash chromatography (eluent: PE/EA: 3/7) to afford compound **8** (0.039 g, 44%) as a white solid. M. p. 162 °C. IR (KBr): 1681 (C = O), 1589, 1538, 1475, 1374, 1143, 1025, 755, 716, 701 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6), δ: 5.29 (s, 2H, CH_2), 6.93–6.96 (m, 2H, CH_{Ar}), 7.21–7.24 (m, 3H, CH_{Ar}), 7.47–7.73 (m, 3H, CH_{Ar}, $CH_{pyridyl}$), 7.94 (d, 1H, ^3J = 7.7 Hz, H-5), 8.20–8.26 (m, 2H, CH_{Ar}, $CH_{pyridyl}$), 8.71 (br s, 2H, $CH_{pyridyl}$). ^{13}C NMR (62.5 MHz, DMSO-d_6), δ: 50.1 (CH_2), 123.4, 125.2, 125.8, 127.2, 127.5 (2 × CH), 128.1, 129.1 (2 × CH), 130.3, 131.2, 133.2, 135.7, 137.5, 137.9, 142.5, 150.2,

152.4, 152.9, 158.0 (C = O), 159.8 (N–C = N). MS (IS), *m/z*: 370.5 $[M + H]^+$. Anal. calcd for $C_{22}H_{15}N_3OS$: C, 71.52; H, 4.09; N, 11.37. Found: C, 71.95; H, 4.18; N, 11.69.

3-Benzyl-2-(3-nitrophenyl)[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (9)

To a solution of compound **2** (0.080 g, 0.193 mmol) in dry THF (10 ml), copper 3-methylsalicylate (0.091 g, 0.424 mmol) and 3-nitrophenylboronic acid (0.071 g, 0.424 mmol) were added. After stirring at room temperature for 10 min, tetrakis(triphenylphosphine) palladium (0.022 g, 0.019 mmol) was added, then the suspension was refluxed for 48 h. The reaction mixture was diluted with dichloromethane and washed with saturated Na_2CO_3 aqueous solution and brine, and finally dried over $MgSO_4$. After filtration, the solvent was removed by evaporation in *vacuo*. The obtained residue was purified by flash chromatography (eluent: PE/EA: 8/2) to afford compound **9** (0.043 g, 54%) as a yellow amorphous solid. IR (KBr): 1676 (C = O), 1531 (Ar-NO_2), 1509, 1453, 1349 (Ar-NO_2), 1145, 757, 747, 733, 704 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6), δ: 5.23 (s, 2H, CH_2), 6.93–6.96 (m, 2H, CH_{Ar}), 7.20–7.34 (m, 3H, CH_{Ar}), 7.59 (t, 1H, ^3J = 7.5 Hz, H-6), 7.67–7.76 (m, 2H, CH_{Ar}), 7.91 (d, 1H, ^3J = 7.5 Hz, H-5), 8.19–8.25 (m, 2H, CH_{Ar}), 8.30 (s, 1H, CH_{Ar}), 8.35 (d, 1H, ^3J = 8 Hz, CH_{Ar}). ^{13}C NMR (62.5 MHz, DMSO-d_6), δ: 48.2 (CH_2), 121.8, 123.2, 123.3, 124.0, 124.6, 125.7, 126.4 (2 × CH), 127.2, 128.4 (2 × CH), 129.3, 130.0, 133.8, 134.5, 136.0, 136.1, 140.6, 147.2, 151.0, 156.3 (C = O), 158.0 (N–C = N). MS (IS), *m/z*: 414.5 $[M + H]^+$. Anal. calcd for $C_{23}H_{15}N_3O_3S$: C, 66.82; H, 3.66; N, 10.16. Found: C, 66.71; H, 3.60; N, 10.03.

CONCLUSIONS

We were able to obtain novel pyrimidin-4-one derivatives from two functionalized starting materials using the modified Stille and Suzuki palladium-catalyzed couplings for the expansion library of potentially biologically active heterocycles. Our experiments clearly demonstrate that Suzuki coupling reactions have considerable advantages. Unexpectedly, the Stille coupling reactions were less productive and some pyridine coupled derivatives were not possible to isolate. On the contrary, the Suzuki approach was much more efficient with the moderate to good yields. Moreover, the boron-containing side products of these transformations were less difficult to remove from the reaction mixture in comparison with the organotin by-products. For these reasons, the Suzuki coupling is more attractive choice than the Stille coupling.

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BENZO- IR TIENOPIRIMIDINONŲ, TURINČIŲ BENZILTIOGRUPĘ, PD-KATALIZUOJAMOS KRYŽMINIO JUNGIMO REAKCIJOS

S a n t r a u k a

Iš 3-benzil-2-(benziltio)chinazolin-4(3*H*)-ono ir 3-benzil-2-(benziltio)[1]benzotieno[3,2-*d*]pirimidin-4(3*H*)-ono darinių, panaudojant Pd-katalizuojamas kryžminio jungimo modifikuotas Suzuki bei Stille reakcijas, susintetinti nauji 2-pakeisti benzeno arba benzotiofeno fragmentus turintys pirimidin-4-ono dariniai. Mūsų atveju, Pd-katalizuojamos Suzuki tipo kryžminio jungimo reakcijos yra daug efektyvesnis metodas įvesti įvairiems pakaitams į pirimidin-4-ono skeletą.