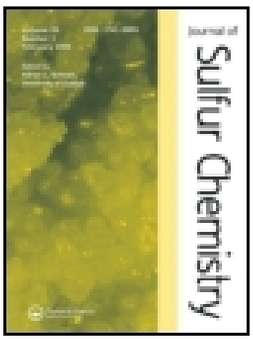


Journal of Sulfur Chemistry

ISSN: 1741-5993 (Print) 1741-6000 (Online) Journal homepage: https://www.tandfonline.com/loi/gsrp20

UV Light-mediated regioselective methylsulfanyl discrimination *via* Pd-catalyzed cross-coupling reactions of 2,4-dimethylsulfanylpyrido[2,3-*d*]pyrimidines

Yassine Riadi

To cite this article: Yassine Riadi (2019): UV Light-mediated regioselective methylsulfanyl discrimination *via* Pd-catalyzed cross-coupling reactions of 2,4-dimethylsulfanylpyrido[2,3-*d*]pyrimidines, Journal of Sulfur Chemistry, DOI: 10.1080/17415993.2019.1590581

To link to this article: https://doi.org/10.1080/17415993.2019.1590581

JOURNAL OF SULFUR CHEMISTRY
https://doi.org/10.1080/17415993.2019.1590581

UV Light-mediated regioselective methylsulfanyl discrimination *via* Pd-catalyzed cross-coupling reactions of 2,4-dimethylsulfanylpyrido[2,3-*d*]pyrimidines

Yassine Riadi

Department of Pharmaceutical Chemistry, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia

ABSTRACT

An effective and novel photochemical method for the preparation of 2,4-disubstituted pyrido[2,3-*d*]pyrimidines is reported from 2,4-dimethylsulfanyl-pyrido[2,3-*d*]pyrimidines through a Liebeskind-Srogl coupling reaction involving an original selective methyl sulfanyl discrimination using UV light as a source of energy. Our strategies involve a two-step and a one-pot approach with reaction times of 11-18 h and yields ranging between 72 and 94%. The two strategies are compared.

ARTICLE HISTORY
Received 19 September 2018
Accepted 24 February 2019

KEYWORDS
Photochemical; pyridopyrimidines; Liebeskind-Srogl; regioselective; methylsulfanyl discrimination

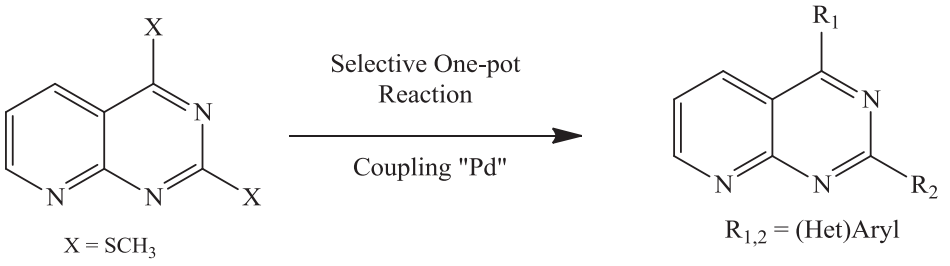
1. Introduction

Palladium-catalyzed reactions including a family of cross-coupling reactions that employ palladium complexes as catalysts [1–3], represent a powerful strategy for the synthesis of highly substituted heterocycles. The selective activation of polyhalogenated heterocycles in such reactions has been extensively investigated [4–8] and can provide a versatile way to prepare libraries of molecules functionalized with different substituents in specific positions of the heterocyclic scaffold.

In the search for new nitrogen-containing biocompatible heterocycles pyridopyrimidines appeared to be very useful candidates. Including pyridopyrimidine in more complex

CONTACT Yassine Riadi yassinriadi@yahoo.fr

This article makes reference to supplementary material available on the publisher's website at https://doi.org/10.1080/17415993.2019.1590581



Scheme 1. General strategy.

molecules has led to a wide range of bioactive scaffolds which can be used as antimicrobial [9], antibacterial [10,11], antifolate [12,13], anti-inflammatory [14,15], insecticidal [16], antiviral [17], anticancer agents [18], antihypertensive [19], antileishmanial [20], anticonvulsants [21], diuretic and potassium-sparing activity [22,23], antituberculostatic [24], antiaggressive [25,26], tyrosine kinase [27] and selective anti-tumoral agents [28]. This explains the interest of chemists in developing strategies and versatile methods to obtain and functionalize them [29].

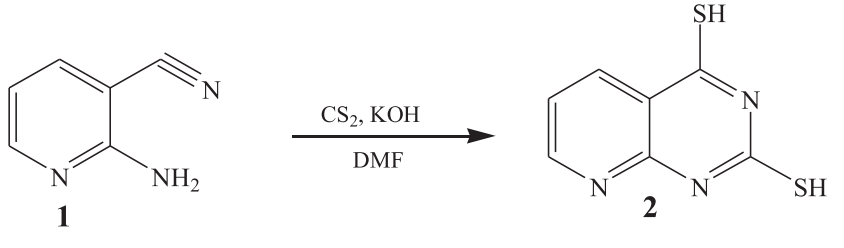
In addition, photo-induced syntheses plays a special role in organic chemistry due to its ecological features and simple and mild reaction conditions, and it has been used as a source of energy for some Pd cross-coupling reaction [30,31].

Based on our previous experience with these heteroaromatic rings and photochemical reactions [32–34] and on other reports of regio- or chemo-selective bis-arylations of related heterocycles [35,36], we decided to develop a new methodology to access a series of isomeric 2,4-disubstituted pyrido[2,3-*d*]pyrimidines *via* cross-coupling reactions (Scheme 1). In the present paper, we report a new method to access bisulfanyl derivative **3** and their first regioselective functionalization by two different strategies using the Liebeskind-Srogl coupling reaction [37–40].

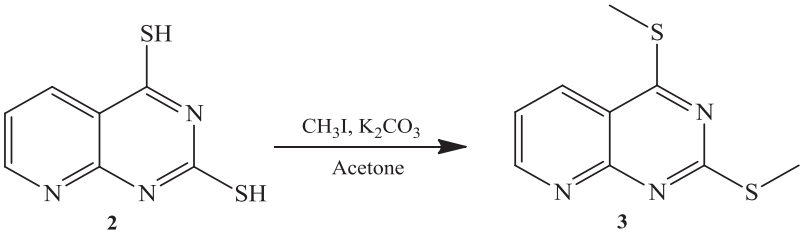
2. Results and discussion

The synthesis of sulfanyl heterocycles has been performed by reacting 2-amino-3-pyridine carbonitrile with carbon disulfide in DMF in the presence of KOH (Scheme 2) [41].

The alkylation of sulfanile heterocycle has been performed starting from compound **2** to obtain the di-sulfide intermediate **3** (Scheme 3) [42].



Scheme 2. Preparation of bis-thiol heterocycle **2**.



Scheme 3. Preparation of bisulfide intermediate **3**.

2.1. Optimization of reaction conditions

Our initial investigation was started with the reaction of compound **3** with phenyl boronic acid under an argon atmosphere in different types of solvents.

In the absence of any light source and catalyst, the product was not obtained (Table 1, entry 1). The reaction was then repeated in presence of $Pd(PPh_3)_4$ as catalyst and CuTC as a cofactor in a glass tube at room temperature in the absence of any source of light, the product also was not obtained (Table 1, entry 2) [32–34]. The reaction was repeated for a third time using a 300 nm wavelength light source, in presence or absence of $Pd(PPh_3)_4$ and CuTC as catalyst and cofactor respectively in a glass tube at room temperature and again the product was not obtained (Table 1, entry 3,4). Furthermore, the reaction was repeated using a 300 nm wavelength light source at room temperature in the presence of different catalysts and solvents. Initially, the desired product was obtained with an isolated yield of 10% in the presence of $Pd(OAc)_2$ as a catalyst (Table 1, entry 6). The product was not obtained when CuMeSal was used as a cofactor (Table 1, entry 5,7). However, the use of $Pd(PPh_3)_4$ in the presence of CuTC increases the yield to 88% (Table 1, entry 13).

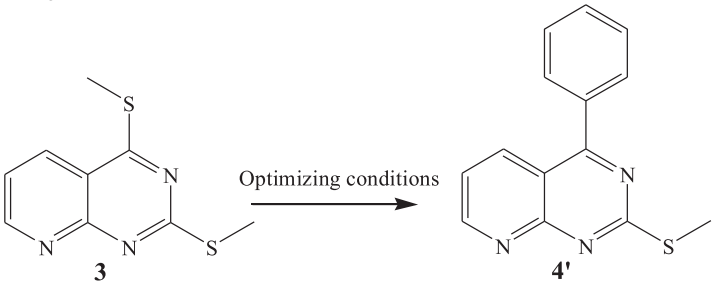
Solvent screening shows that the reaction in DMF gives the best yield (88%), in comparison with other solvents, like DMSO, THF, MeCN, $CHCl_3$or acetone (Table 1, entries 7-13). Optimization studies showed that light is needed for the reaction and that the yield of the reaction is wavelength dependent (Table 1, entries 14, 15). Air significantly diminishes the yield to 20% (Table 1, entry 16) and suggests that an argon atmosphere is essential for the success of the reaction.

2.2. Application of the methodology

Having in hand the optimal conditions, we first studied the scope of the reaction, by reacting compounds **3** under Liebeskind-Srogl cross-coupling reaction conditions [43]. We were able to obtain regioselective arylation at *C4*. Reacting the disulfide **3** and a stoichiometric amount of phenylboronic acid using $Pd(PPh_3)_4$ (5 mol%) as catalyst in presence of CuTC and DMF, we observed that the starting compound **3** was totally consumed and only the monoarylated derivative **4′** was formed in a good yield (89%) and no trace of substituted product has been observed (Table 2, Entry 1; Column 3).[1]

After this result, we decided to generate the monoarylated derivatives by reaction between compound **3** and different boronic acids. The heteroaryl (Het)Ar[1] were successfully introduced and the monoarylated derivatives were obtained after purification by

Table 1. Optimizing conditions of reaction.[a]



3 4'

Entry	Catalyst	Cofactor	*Hv*	Solvent	Yields (%) (Time)
1	–	–	–	DMF	0 (24 h)
2	$Pd(PPh_3)_4$	CuTC	–	DMF	0 (24 h)
3	$Pd(PPh_3)_4$	–	300 nm	DMF	0 (24 h)
4	–	CuTC	300 nm	DMF	0 (24 h)
5	$Pd(OAc)_2$	CuMeSal	300 nm	DMF	0 (9 h)
6	$Pd(OAc)_2$	CuTC	300 nm	DMF	10 (9 h)
7	$Pd(PPh_3)_4$	CuMeSal	300 nm	MeCN	0 (9 h)
8	$Pd(PPh_3)_4$	CuTC	300 nm	MeCN	60 (9 h)
9	$Pd(PPh_3)_4$	CuTC	300 nm	THF	41(9 h)
10	$Pd(PPh_3)_4$	CuTC	300 nm	DMSO	18 (9 h)
11	$Pd(PPh_3)_4$	CuTC	300 nm	acetone	26 (9 h)
12	$Pd(PPh_3)_4$	CuTC	300 nm	$CHCl_3$	34 (9 h)
13	$Pd(PPh_3)_4$	CuTC	300 nm	DMF	89 (8 h)
14	$Pd(PPh_3)_4$	CuTC	> 280 nm	DMF	41 (8 h)
15	$Pd(PPh_3)_4$	CuTC	Visible light	DMF	58 (8 h)
16[c]	$Pd(PPh_3)_4$	CuTC	300 nm	DMF	20 (8 h)

[a]Yield of pure isolated product. Reaction conditions: $C_6H_5B(OH)_2$, $Pd(PPh_3)_4$ (5 mol %), DMF (5 mL), CuTC, *hv,* under argon atmosphere.
[b]Isolated yields.
[c]Reaction run in air.

chromatography on silica gel. The yields of isolated products ranged between 76 and 89% for a reaction time of 8–9 h (Table 2).

Then, the monoarylated products were engaged in a second Liebeskind-Srogl coupling reaction to afford to the diarylated derivatives **4.**[2] The second heteroaryl groups, (Het)Ar^2, were successfully introduced and the expected products were obtained after purification by chromatography on silica gel. Yields of isolated products oscillated between 72 and 90% in a total reaction time of 16–18 h (Table 2; Columns 4, 5, and 6).

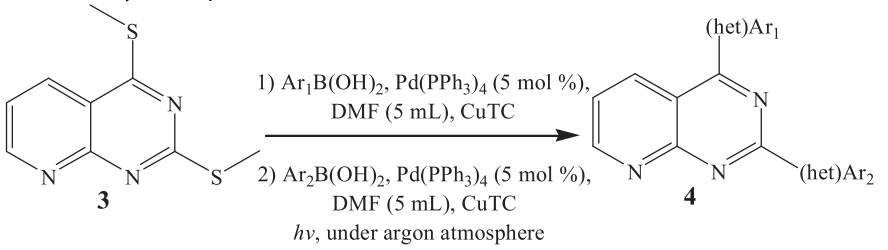
We then envisioned a one-pot arylation at the *C2* and *C4* position. The ethanol was used as co-solvent to get the best yield (Table 3).[3]

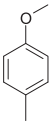
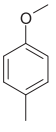
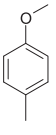
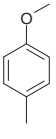
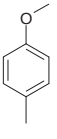
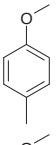
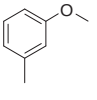
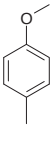
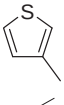
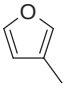
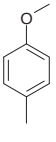
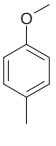
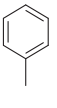
The two heteroaryl (Het) Ar_1 and (Het) Ar_2 were successfully introduced and the expected heterocycles were obtained after purification by chromatography on silica gel. The yields of isolated products ranged between 77 and 94% for a reaction time of 11–13 h (Table 3). This one-pot method, compared to the two-step strategy, produced the products in approximately the same yields but in less time. This result proves the importance of the one-pot strategy.

Structure of final product **4a** was determined by X-ray analysis (Figure 1).

Based on the studies by Handy and co-authors, we can justify the order and site of the coupling using the ^1H NMR chemical shift values of the parent non-sulfited heteroaromatics. Indeed, we found that palladium cross-coupling reactions were carried

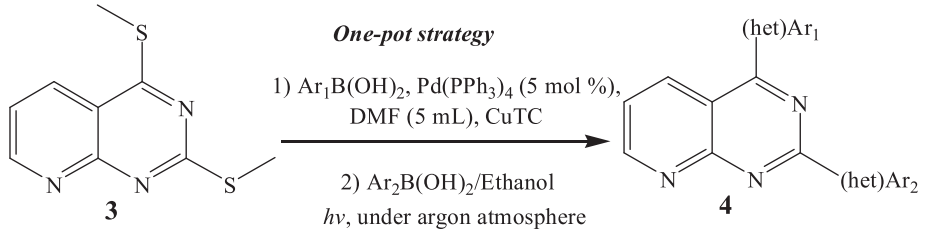
Table 2. Reactivity of compounds **3** with different boronic acids.

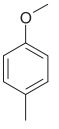
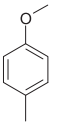
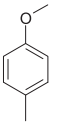
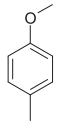
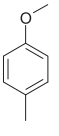
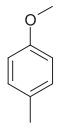
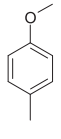
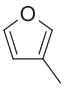
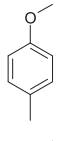
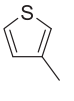
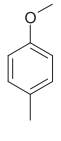
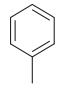


Entry	(het)Ar_1	Yields of monoarylated[b] (%) (Time (h))	(het)Ar_2	Products	Yields[b] (%) (Time)
1		89 (8 h)		**4a**	90 (8 h)
2		86 (8 h)		**4b**	84 (8 h)
3		76 (8 h)		**4c**	76 (8 h)
4		88 (9 h)		**4d**	74 (8 h)
5		88 (9 h)		**4e**	85 (9 h)
6		88 (9 h)		**4f**	78 (10 h)
7		76 (8 h)		**4g**	72 (10 h)
8		88 (9 h)		**4h**	84 (10 h)
9		88 (9 h)		**4i**	78 (9 h)

[a]Yields are given for isolated products.

Table 3. Reactivity of di-sulfide compound **3** with different boronic acids.



Entry	(het)Ar_1	(het)Ar_2	Products	Yields[b] (%) (Time)
1			**4a**	94 (11 h)
2			**4b**	87 (11 h)
3			**4c**	79 (11 h)
4			**4d**	77 (11 h)
5			**4e**	89 (13 h)
6			**4f**	82 (13 h)
7			**4g**	78 (13 h)
8			**4h**	90 (13 h)
9			**4i**	86 (13 h)

[a]Yields are given for isolated products.

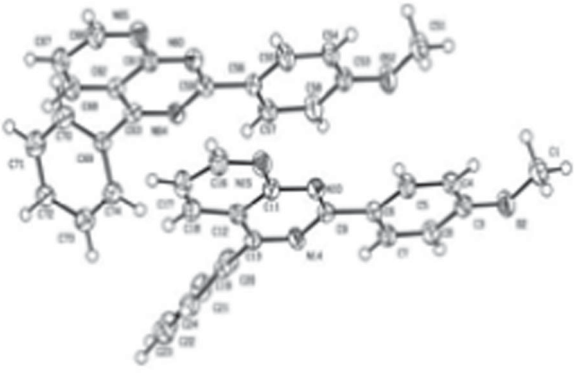


Figure 1. Ortep of compound **4a**.

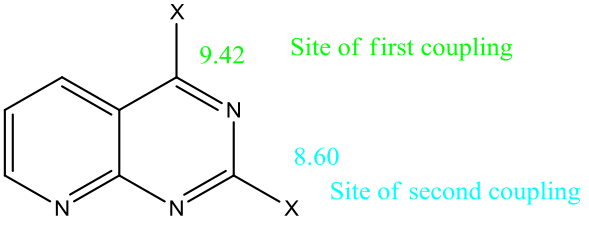


Figure 2. Cross-coupling order based upon the ^{1}H NMR chemical shift values.

out successively in the sequence *C4* first and *C2* second (Figure 2) [44], which means that the carbon with the most deshielded proton is the most reactive carbon.

The current research describes the first photochemical access to 2,4-disubstituted pyrido[2,3-*d*]pyrimidine and its first use to build substituted pyrido[2,3-*d*]pyrimidines using a novel and highly effective strategy. An efficient and simple strategy was adopted to prepare highly substituted pyrido[2,3-*d*]pyrimidines which facilitate the orchestration of selective palladium-catalyzed cross-coupling reactions for the preparation of focused libraries of biologically active compounds. The one-pot and step-by-step processes were synthetically compared. The great value of the one-pot methodology is a result of good yields and fast turnover.

Notes

1. General procedure for the synthesis of **4**: A solution containing 2,4-dimethylsulfanylpyrido[2,3-*d*]pyrimidine **3** (0.35 mmol), the (het)aryl boronic acid (1.1 equiv), CuTC (2.2 equiv) and $Pd(PPh_3)_4$ (0.05 equiv) in dry DMF (5 mL) was flushed with argon for 15 min. The brown suspension was irradiated under argon for 8 h. After complete disappearance of starting material **3**, a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with saturated NaHCO3 (2 × 10 mL). The solvent were evaporated under reduced pressure the residue was next purified by flash chromatography to give the attempted monoarylated products. General procedure for the synthesis of **4′** *via* Liebeskind-Srogl cross-coupling reaction:
2. A solution containing 4-heteroaryl-2-methylsulfanylpyrido[2,3-*d*]pyrimidine **4′** (0.35 mmol), the (het)aryl boronic acid (2.2 equiv), CuTC (2.2 equiv) and $Pd(PPh_3)_4$ (0.05 equiv) in dry

DMF (5 mL) was flushed with argon for 15 min. The brown suspension was irradiated under argon for 8 h. After complete disappearance of starting material **4′**, a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 10 mL). The solvent were evaporated under reduced pressure the residue was next purified by flash chromatography to give the attempted biarylated products types **4**. **4-Phenyl-2-(4-methoxyphenyl)pyrido[2,3-*d*]pyrimidine 4a:** was isolated after flash chromatography (DCM) as a white solid. Mp 128-130°C; IR (ATR-Ge, cm^{-1}) ν 1592, 1456, 1314, 1262, 1078, 914, 856, 789; ^{1}H RMN (250 MHz, $CDCl_3$) δ 3.92 (s, 3H, OCH_3), 7.12 (d, J = 7.5 Hz, 2H, H_{Ar}), 7.50 (m, 4H, J = 2.5, 7.5 Hz, $H_{Ar,}$ H_6), 7.86 (dd, 2H, J = 2.5, 7.5 Hz, H_{Ar}), 8.51 (d, 1H, J = 7.5 Hz, H_5), 8.80 (dd, 2H, J = 2.5, 7.5 Hz, H_{Ar}), 9.21 (d, 1H, J = 2.5 Hz, H_7); ^{13}C RMN (62.5 MHz, $CDCl_3$) δ 55.66 (CH_3), 114.33 (2 × CH), 116.32 (Cq), 122.25 (CH), 128.55 (2 × CH), 129.20 (Cq), 129.28 (2 × CH), 131.28 (CH), 132.03 (2 × CH), 136.52 (CH), 137.48 (Cq), 157.44 (CH), 160.08 (Cq), 161.78 (Cq), 163.49 (Cq), 169.46 (Cq); HRMS (EIMS): m/z calcd for $C_{20}H_{15}N_3O$: 314.1287, found: 314.1289.

3. General procedure for the one-pot synthesis of **3** *via* Liebeskind-Srogl cross-coupling reaction: A solution containing 2,4-bimethylsulfanylpyrido[2,3-*d*]pyrimidine **3** (0.35 mmol), the (het)aryl boronic acid (1.1 equiv), CuTC (2.2 equiv) and $Pd(PPh_3)_4$ (0.05 equiv) in dry DMF (5 mL) was flushed with argon for 15 min. The brown suspension was irradiated under argon. After complete disappearance of starting material **3**, the second (het)aryl boronic acid (1.5 equiv) dissolved in ethanol and added to the reaction. After complete of reaction, a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 10 mL). The solvent were evaporated under reduced pressure the residue was next purified by flash chromatography to give the attempted biarylated products types **4**. **2-(4-Methoxyphenyl)-4-(3-thienyl)pyrido[2,3-*d*]pyrimidine 4c:** was isolated after flash chromatography (DCM) as a white solid. Mp 182–184°C; IR (ATR-Ge, cm^{-1}) ν 1616, 1522, 1436, 1382, 1334, 1204, 944, 747 ; ^{1}H RMN (250 MHz, $CDCl_3$) δ 3.89 (s, 3H, OCH_3), 7.08 (d, 2H, J = 8.0 Hz, H_{Ar}), 7.37 (d, 1H, J = 8.0 Hz, H_{Het}), 7.42 (dd, 1H, J = 4.0, 8.0 Hz, H_6), 7.80 (d, 2H, J = 8.0 Hz, H_{Ar}), 8.16 (d, 1H, J = 4.0 Hz, H_{Het}), 8.44 (d, 1H, J = 8.0 Hz, H_5), 8.58 (dd, 1H, J = 4.0, 8.0 Hz, H_{Het}), 9.15 (d, 1H, J = 4.0 Hz, H_7); ^{13}C RMN (62.5 MHz, $CDCl_3$) δ 55.50 (CH_3), 114.25 (2 × CH), 116.06 (Cq), 121.96 (CH), 125.90 (CH), 128.19 (CH), 128.96 (Cq), 129.94 (CH), 131.90 (2 × CH), 136.50 (CH), 141.81 (Cq), 157.30 (CH), 159.97 (Cq), 160.46 (Cq), 161.71 (Cq), 169.51 (Cq); HRMS (EIMS): m/z calcd for $C_{18}H_{13}N_3OS$: 320.0858, found: 320.0854.

Acknowledgment

The authors would like to thank the College of Pharmacy at Prince Sattam Bin Abdulaziz University for providing the necessary facilities to carry out this research work.

Disclosure statement

No potential conflict of interest was reported by the author.

References

[1] Peng Z, Hu G, Qiao H, et al. Palladium-catalyzed Suzuki cross-coupling of arylhydrazines via C–N bond cleavage. J Org Chem. 2014;79:2733–2738.
[2] Duda ML, Michael FE. Palladium-catalyzed cross-coupling of N-Sulfonylaziridines with boronic acids. J Am Chem Soc. 2013;135:18347–18349.
[3] Kalinin VN. Carbon-carbon bond formation in heterocycles using Ni- and Pd-catalyzed reactions. Synthesis (Mass). 1992: 413–432.
[4] Schröter S, Stock C, Bach T. Regioselective cross-coupling reactions of multiple halogenated nitrogen-, oxygen-, and sulfur-containing heterocycles. Tetrahedron. 2005;61:2245–2267.

[5] Theeramunkong S, Caldarelli A, Massarotti A, et al. Regioselective Suzuki coupling of dihaloheteroaromatic compounds as a rapid strategy to synthesize potent rigid combretastatin analogues. J Med Chem. 2011;54:4977–4986.
[6] Parks EL, Sandford G, Christopher JA, et al. Perhalogenated pyrimidine scaffolds. Reactions of 5-chloro- 2,4,6-trifluoropyrimidine with nitrogen centred nucleophiles. Beilstein J. Org. Chem. 2008;4:22–28.
[7] Tumkevicius S, Dodonova J. Functionalization of pyrrolo[2,3-d]pyrimidine by palladium-catalyzed cross-coupling reactions (review). Chem Heterocycl Comp. 2012;48:258–279.
[8] Skardziute L, Dodonova J, Voitechovicius A, et al. Synthesis and optical properties of the isomeric pyrimidine and carbazole derivatives: effects of polar substituents and linking topology. Dyes Pigm. 2015;118:118–128.
[9] Reck F, Alm R, Brassil P, et al. Novel N-linked aminopiperidine inhibitors of bacterial topoisomerase type II: broad-spectrum antibacterial agents with reduced hERG activity. J Med Chem. 2011;54:7834–7847.
[10] Rajesh SM, Kumar RS, Libertsen LA, et al. A green expedient synthesis of pyridopyrimidine-2-thiones and their antitubercular activity. Bioorg Med Chem Lett. 2011;21:3012–3016.
[11] Ribble W, Hill WE, Ochsner UA, et al. Mechanisms of action: physiological effects discovery and analysis of 4*H*-pyridopyrimidines, a class of selective bacterial protein synthesis inhibitors. Antimicrob Agents Chemother. 2010;54:4648–4657.
[12] Rosowsky A, Mota CE, Queener SF. Synthesis and antifolate activity of 2,4-diamino-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine analogues of trimetrexate and piritrexim. J Heterocyclic Chem. 1995;32:335–340.
[13] Grivsky EM, Lee S, Sigel CW, et al. Synthesis and antitumor activity of 2,4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-*d*]pyrimidine. J Med Chem. 1980;23:327–329.
[14] Nofal ZM, Fahmy HH, Zarea ES, et al. Synthesis of new pyrimidine derivatives with evaluation of their anti-inflammatory and analgesis activities. Acta Pol Pharm. 2011;68:507–517.
[15] Ghilsoo N, Cheol MY, Euikyung K, et al. Syntheses and evaluation of pyrido[2,3-*d*]pyrimidine-2,4-diones as PDE 4 inhibitors. Bioorg Med Chem Lett. 2001;11:611–614.
[16] Singh G, Singh G, Yadav AK, et al. Synthesis and antimicrobial evaluation of some new pyrido[2,3-*d*]pyrimidines and their ribofuranosides. Indian J Chem Sect B: Org Chem Incl Med Chem. 2002;41:430–432.
[17] Liu KK, Huang X, Bagrodia S, et al. Quinazolines with intra-molecular hydrogen bonding scaffold (iMHBS) as PI3 K/mTOR dual inhibitors. Bioorg Med Chem Lett. 2011;21:1270–1274.
[18] El-Subbagh HI, Abu-Zaid SM, Mahran MA, et al. Synthesis and biological evaluation of certain α,β-unsaturated ketones and their corresponding fused pyridines as antiviral and cytotoxic agents. J Med Chem. 2000;43:2915–2921.
[19] Bennett LR, Blankley CJ, Fleming RW, et al. Antihypertensive activity of 6-arylpyrido[2,3-*d*]pyrimidin-7-amine derivatives. J Med Chem. 1981;24:382–389.
[20] Agarwal A, Ramesh R, Ashutosh A, et al. Dihydropyrido[2,3-*d*]pyrimidines as a new class of antileishmanial agents. Bioorg Med Chem. 2005;13:6678–6684.
[21] Mahmoud MR, El-Bordany EAA, Hassan NF, et al. Utility of nitriles in synthesis of pyrido[2,3-*d*]pyrimidines, thiazolo[3,2-*a*]pyridines, pyrano[2,3-*b*]benzopyrrole, and pyrido[2,3-*d*]benzopyrroles. Phosphorus Sulfur Silicon Relat. Elem. 2007;182:2507–2521.
[22] Bulicz J, Daniela CG, Bertarelli DCG, et al. Synthesis and pharmacology of pyrido[2,3-*d*]pyrimidinediones bearing polar substituents as adenosine receptor antagonists. Bioorg. Med. Chem. 2006;14:2837–2849.
[23] Monge A, Martinez-Merino V, Sanmartin C, et al. 2-Arylamino-4-oxo-3,4-dihydropyrido[2,3-*d*]pyrimidines: synthesis and diuretic activity. Eur J Med Chem. 1989;24:209–216.
[24] El-Gazzar ABA, Gaffar AM, Youssef MM, et al. Synthesis and anti-oxidant activity of novel pyrimido[4,5-*b*]quinolin-4-one derivatives with a new ring system. Phosphorus Sulfur Silicon Relat Elem. 2007;182:2009–2037.

[25] Taylor EC, Palmer DC, George TJ, et al. Synthesis and biological activity of L-5-deazafolic acid and L-deazaaminopterin: synthetic strategies to 5-deazapteridines. J Org Chem. 1983;48:4852–4860.
[26] Degraw JI, Christie PH, Colwell WT, et al. Synthesis and antifolate properties of 5,10-ethano-5,10-dideazaaminopterin. J Med Chem. 1992;35:320–324.
[27] Saurat T, Buron F, Rodrigues N, et al. Design, synthesis, and biological activity of pyridopyrimidine scaffolds as novel PI3 K/mTOR dual inhibitors. J Med Chem. 2014;57:613–631.
[28] Font M, González Á, Palop JA, et al. New insights into the structural requirements for pro-apoptotic agents based on 2,4-diaminoquinazoline, 2,4-diaminopyrido[2,3-*d*]pyrimidine and 2,4-diaminopyrimidine derivatives. Eur J Med Chem. 2011;46:3887–3899.
[29] Sako M. In Science of Synthesis. Vol. 16. Yamamoto Y, editor. Thieme: Stuttgart; 2004. p. 1155.
[30] Mitchell LJ, Lewis W, Moody CJ. Solar photochemistry: optimisation of the photo Friedel-Crafts acylation of naphthoquinones. Green Chem. 2013:15:2830.
[31] Ravelli D, Fagnoni M, Albini A. Photoorganocatalysis what for? Chem Soc Rev. 2013;42:97–113.
[32] Riadi Y, Massip S, Leger JM, et al. Convenient synthesis of 2,4-disubstituted pyrido[2,3-*d*]pyrimidines via regioselective palladium-catalyzed reactions. Tetrahedron. 2012;68:5018–5024.
[33] Riadi Y, Geesi M, Dehbi O, et al. Novel animal-bone-meal-supported palladium as a green and efficient catalyst for Suzuki coupling reaction in water, under sunlight. Green Chem Lett Rev. 2017;10:101–106.
[34] Riadi Y, Geesi M. Photochemical route for the synthesis of novel 2-monosubstituted pyrido[2,3-*d*]pyrimidines by palladium-catalyzed cross-coupling reactions. Chem Pap. 2018;72:697–701.
[35] Krömer M, Klečka M, Slavětínská L, et al. Chemoselective synthesis of 4,5-diarylpyrrolo[2,3-*d*]pyrimidines (6,7-diaryl-7-deazapurines) by consecutive Suzuki and Liebeskind-Srogl cross-couplings. Eur J Org Chem. 2014;32:7203–7210.
[36] Čerňová M, Pohl R, Klepetářová B, et al. A general regioselective synthesis of 2,4-diarylpyrimidines from 2-Thiouracil through two orthogonal cross-coupling reactions. Synlett. 2012;23:1305–1308.
[37] Liebeskind LS, Srogl J. Thiol ester—boronic acid coupling. A Mechanistically unprecedented and general ketone synthesis. J. Am. Chem. Soc. 2000;122:11260–11261.
[38] Liebeskind LS, Srogl J. Heteroaromatic thioether—boronic acid cross-coupling under neutral reaction conditions. Org. Lett. 2002;4:979–981.
[39] Egi M, Liebeskind LS. Heteroaromatic thioether—organostannane cross-coupling. Org. Lett. 2003;5:801–802.
[40] Maingot L, Dehbi O, Buron F, et al. Regioselective syntheses of 2,7-(Het)arylpyrido[2,3-d]pyrimidines by an orthogonal cross-coupling. Strategy. 2012;23:2449–2452.
[41] El-Remaily MAA, El Hady OM, Abo Zaid HS, et al. Synthesis and in vitro antibacterial activity of some novel fused pyridopyrimidine derivatives. J Heterocyclic Chem. 2016;53:1304–1309.
[42] Abdel-Mohsen SA, Geies AA. Synthesis of pyrido[2′,3′:4,5]thieno[2,3-d]pyrimidines through Friedländer reactions. J Chem Res. 2007;12:689–692.
[43] Yu Y, Liebeskind LS. Copper-mediated, palladium-catalyzed coupling of thiol esters with aliphatic organoboron reagents. J Org Chem. 2004;69:3554–3557.
[44] Handy ST, Zhang Y. A simple guide for predicting regioselectivity in the coupling of polyhaloheteroaromatics. Chem Commun. 2006;299–301.