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Renaissance of 4-(5-nitrofuran-2-yl)-5-arylamino substituted pyrimidines: microwave-assisted synthesis and antitubercular activity

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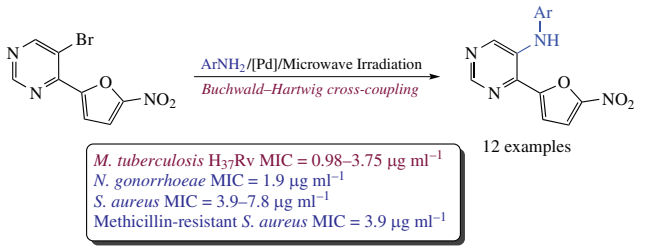
The Buchwald–Hartwig cross-coupling of 5-bromo-4-(furan-2-yl)pyrimidine with various anilines afforded the corresponding new 5-(arylamino)pyrimidines, the reaction being accelerated by microwave irradiation. Most of the obtained compounds proved to possess a high bacteriostatic *in vitro* effect against *Mycobacterium tuberculosis* $H_{37}Rv$, *Neisseria gonorrhoeae*, and *Staphylococcus aureus* including Methicillin-resistant strain, which is stronger than that of the commercial drug Spectinomycin.



Keywords: pyrimidines, nitrofurans, anti-mycobacterial activity, Buchwald–Hartwig amination, cross-coupling reactions.

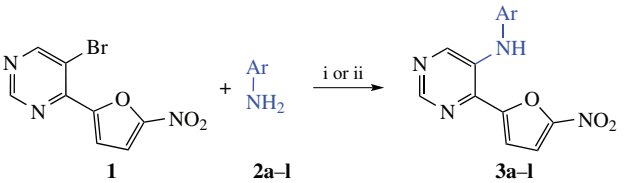
For nearly the whole year 2020, the major world infection has been the coronavirus known as SARS-CoV-2.[1,2] Obviously, the main forces of scientists have been directed to develop new anti-virus agents to combat this pandemic.[3–6] On the other hand, concomitant bacterial infections are commonly identified in viral respiratory tract infections such as COVID-19. They become an important cause of morbidity and mortality, necessitating timely diagnosis, and antibacterial therapy.[7] One of the most dangerous bacterial infections appears to be tuberculosis that claims the lives of around 1.7 million people with 10.4 million infections reported per year.[8] The appearance and increasing number of *Mycobacterium tuberculosis* (*Mtb*) strains with multiple drug resistance, as well as a growing number of other bacterial infections that are not sensitive to antibiotics should be regarded as a serious threat to public healthcare. Therefore, no doubt that the development of novel antimicrobial agents for the treatment of infectious diseases caused by various bacteria strains is an urgent priority of medicinal chemistry.[9] Nitrofuran derivatives are known to be highly effective in both antibacterial and anti-tuberculosis agents.[10–13] Previously,[14] we have described a series of pyrimidine conjugating nitrofurans which had a high level of inhibition against various *Neisseria gonorrhoeae*, *Streptococcus pyogenes*, and *Staphylococcus aureus* strains. These compounds were obtained by the Buchwald–Hartwig C–N coupling of 5-bromo-4-(5-nitrofuran-2-yl)pyrimidine **1** with the corresponding anilines in the presence of 20 mol% $Pd(OAc)_2$ and 40 mol% dppf as the ligand at 85 °C for 15 h (Scheme 1, conditions i).

In this work, we intended to perform the arylamination of 5-bromo-4-(furan-2-yl)pyrimidine **1** with various anilines through the microwave-assisted Buchwald–Hartwig amination and to test the thus obtained compounds toward their *in vitro* antimicrobial activities against *M. tuberculosis* $H_{37}Rv$ bacteria and some other bacteria.

At the first stage, we have optimized the microwave-assisted procedure employing aniline **2a** as the model substrate (Table 1).[15] In our previous work,[14] dppf, a bidentate phosphine ligand, provided the best yields of the target compound **3a** (see Table 1, entry 1).[14] Herein, good yields up to 61% were also achieved with dppf (entries 2–4). Nonetheless, the highest yield 77% of **3a** has been observed when Xantphos was used as ligand (entry 6 *vs.* 4).

Based on the above results, the structural diversity of various substituted anilines **2a–l** was examined (see Scheme 1, conditions ii) to afford the corresponding 4-(5-nitrofuran-2-yl)-5-arylamino substituted pyrimidines **3a–l**. As can be seen, the electronic character of the substituents in anilines does not have any effect on their reaction activity. In all cases, the desired products **3a–l** were prepared in good yields of 43–85%, thus exceeding the previously reported[14] values (see Scheme 1, conditions ii *vs.* i).

Notably, bromination can be used to readily improve the antimicrobial activity against Gram-positive bacteria.[16] To



a Ar = Ph
b Ar = 2-MeC_6H_4
c Ar = 3-MeC_6H_4
d Ar = 4-MeC_6H_4
e Ar = 2-$MeOC_6H_4$
f Ar = 3-$MeOC_6H_4$
g Ar = 4-$MeOC_6H_4$
h Ar = 3,4-$(MeO)_2C_6H_3$
i Ar = 3,4,5-$(MeO)_3C_6H_2$
j Ar = 2-$O_2NC_6H_4$
k Ar = 3-$O_2NC_6H_4$
l Ar = 4-$O_2NC_6H_4$

Scheme 1 *Reagents and conditions*: i, $Pd(OAc)_2$ (20 mol%), dppf (40 mol%), K_3PO_4 (2.5 equiv.), 85 °C, 15 h (see ref. 14); ii, $Pd(OAc)_2$ (10 mol%), Xantphos (20 mol%), K_3PO_4 (2.5 equiv.), MW (250 W), 150 °C, 10 min.

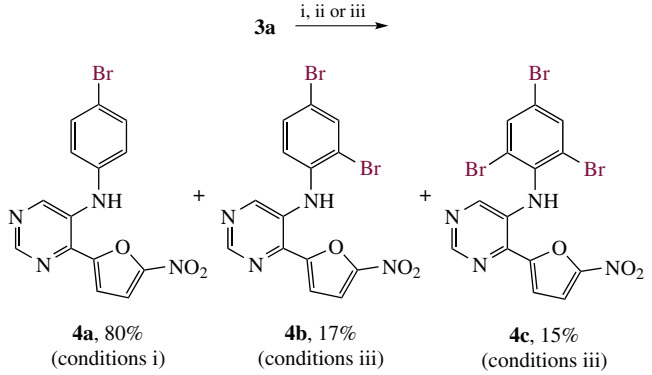
Table 1 The Buchwald–Hartwig amination of bromopyrimidine **1** with anilines **2a–l**.[a]

Entry	$ArNH_2$	Ligand[b]	MW[c]	*T*/°C	*t*	Product	Yield (%)
1	**2a**	dppf	no	85	15 h	**3a**	56
2	**2a**	dppf	yes	150	40 min	**3a**	25 (31)[d]
3	**2a**	dppf	yes	150	20 min	**3a**	33 (14)[e]
4	**2a**	dppf	yes	150	10 min	**3a**	61 (39)[f]
5	**2a**	XPhos	yes	150	10 min	**3a**	21
6	**2a**	Xantphos	yes	150	10 min	**3a**	77 (71)[f]
7	**2b**	dppf/Xantphos	no/yes	85/150	15 h/10 min	**3b**	– /65
8	**2c**	dppf/Xantphos	no/yes	85/150	15 h/10 min	**3c**	47/82
9	**2d**	dppf/Xantphos	no/yes	85/150	15 h/10 min	**3d**	67/68
10	**2e**	dppf/Xantphos	no/yes	85/150	15 h/10 min	**3e**	– /67
11	**2f**	dppf/Xantphos	no/yes	85/150	15 h/10 min	**3f**	35/71
12	**2g**	dppf/Xantphos	no/yes	85/150	15 h/10 min	**3g**	45/85
13	**2h**	dppf/Xantphos	no/yes	85/150	15 h/10 min	**3h**	55/79
14	**2i**	dppf/Xantphos	no/yes	85/150	15 h/10 min	**3i**	50/84
15	**2j**	dppf/Xantphos	no/yes	85/150	15 h/10 min	**3j**	29/42
16	**2k**	dppf/Xantphos	no/yes	85/150	15 h/10 min	**3k**	53/54
17	**2l**	dppf/Xantphos	no/yes	85/150	15 h/10 min	**3l**	58/63

[a] The molar ratio **1/2** is 1 : 1.2, K_3PO_4 (2.5 equiv.), dioxane; entries 7–17 stand for the data of two alternative procedures without or with MW irradiation. [b] dppf is 1,1′-bis(diphenylphosphino)ferrocene; Xantphos is 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; XPhos is 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. [c] Without MW, 20 mol% $Pd(OAc)_2$ and 40 mol% dppf (see ref. 12); with MW, 10 mol% $Pd(OAc)_2$ and 20 mol% ligand. [d] At 110 °C. [e] Reaction time 5 min. [f] With 40 mol% ligand.

explore an opportunity of further modification of compounds **3**, we have studied the bromination of the representative **3a** by application of *N*-bromosuccinimide (NBS) at room temperature for 24 h in DMF (Scheme 2, see also Online Supplementary Materials, Table S1). In fact, the reaction of **3a** with 1 equiv. NBS gave only monobromination product **4a** in 80% yield. Polybromination of **3a** with more NBS to afford 2,4-dibromo (**4b**, 17%) and 2,4,6-tribromo (**4c**, 11%) derivatives proceeded much less efficiently and regioselectively. However, we managed to isolate each of compounds **4a**,**b**,**c** in an individual state.

The series of compounds **3a–i** was screened for their *in vitro* activities against *M. tuberculosis* $H_{37}Rv$ (Table 2) by exploiting the Resazurin reduction assays procedure.[17] Compounds **3j–l** were not tested towards *M. tuberculosis* $H_{37}Rv$ because they had just displayed *in vitro* a high level of cytotoxicity.[14] All the tested compounds (with the exception for **3i)** are active at MIC from 3.75 to 0.47 μg ml^{-1}. It should be noted that pyrimidines **3c**,**f** bearing *meta* Me or OMe substituents in benzene moiety which exhibited earlier the highest activities against *S. pyogenes* and *S. aureus* strains, herein were also the most effective (up to 0.47 μg ml^{-1}) against *M. tuberculosis* $H_{37}Rv$ (see Table 2, entries 3 and 6). Pyrimidines **3b**,**e** with *ortho* Me or OMe groups and bromo substituted derivatives **4a–c** were explored for their *in vitro* activities against fourteen strains of gram-negative



Scheme 2 *Reagents and conditions*: i, NBS (1 equiv.), room temperature, 24 h; ii, NBS (2 equiv.), room temperature, 24 h; iii, NBS (3 equiv.), room temperature, 24 h.

(*N. gonorrhoeae*, *E. coli*, *C. braakii*, *S. flexneri*, *P. vulgaris*, *S. marcescens*, *K. pneumoniae* and *P. aeruginosa*) and gram-positive (*S. pyogenes* and *S. aureus*) bacteria using previously described experimental procedure.[14] They proved to exhibit a high level of activity only against *Staphylococcus aureus* including Methicillin-resistant strain (entries 2, 5, 13 and 14). Also, bromo derivatives **4a–c** were most effective at concentration of 1.9 μg ml^{-1} against *N. gonorrhoeae* (entries 13–15). Thus,

Table 2 *In vitro* antibacterial activity of *N*-aryl-4-(5-nitrofuran-2-yl)-pyrimidin-5-amines **3a–l** and **4a–c**.

Entry	Compound	Antibacterial activity (MIC)/μg ml^{-1}			
		Mbt $H_{37}Rv$	*N. gonorrhoeae* NCTC 8375/ ATCC 19424	*S. aureus*	*S. aureus* MRSA
1	**3a**	1.88	1.9[a]	3.9[a]	1.9[a]
2	**3b**	3.75	15.6	3.9	3.9
3	**3c**	0.94	7.8[a]	7.8[a]	0.9[a]
4	**3d**	1.88	1.9[a]	15.6[a]	125[a]
5	**3e**	3.75	15.6	7.8	3.9
6	**3f**	0.47	7.8[a]	7.8[a]	3.9[a]
7	**3g**	1.88	3.9[a]	125[a]	125[a]
8	**3h**	1.88	3.9[a]	3.9[a]	15.6[a]
9	**3i**	15.0	0.9[a]	62.5[a]	7.8[a]
10	**3j**	n.d.	500[a]	>1000[a]	>1000[a]
11	**3k**	n.d.	7.8[a]	250[a]	250[a]
12	**3l**	n.d.	62.5[a]	62.5[a]	62.5[a]
13	**4a**	n.d.	**1.9**	>250	**3.9**
14	**4b**	n.d.	**1.9**	**3.9**	**3.9**
15	**4c**	n.d.	**1.9**	62.5	>250
16	INH	0.03	–	–	–
17	SPEC	–	15.6	31.25	>250

[a] Previously published antibacterial data;[14] n.d. – not determined; INH – Isoniazid; SPEC – Spectinomycin; ATCC – American Type Culture Collection; RCPM – Russian Collection of Pathogenic Microorganisms. *Mbt* $H_{37}Rv$ – *Mycobacterium tuberculosis* $H_{37}Rv$ ATCC 27294; *N. gonorrhoeae* NCTC 8375/ATCC 19424 – *Neisseria gonorrhoeae* NCTC 8375/ATCC 19424; *S. aureus* – *Staphylococcus aureus* NCTC 12981 (F-49)/ ATCC 25923; *S. aureus* MRSA – Methicillin-resistant *Staphylococcus aureus* NCTC 12493.

most of the synthesized compounds may be regarded as scaffolds for the design of the next generation analogs of '(5-nitrofuran-2-yl)-diazine' antitubercular and antibacterial agents.[18,19]

In conclusion, we have developed an expedient microwave-assisted synthesis of *N*-aryl-4-(5-nitrofuran-2-yl)pyrimidin-5-amines that could be obtained 90 times faster (10 min *vs.* 15 h) and in higher yields. Being not active enough to be therapeutics, these compounds can be regarded as promising structures for further elucidations aimed at the development of novel effective agents to combat resistant forms of *M. tuberculosis* and other bacterial strains.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.021.

References

1 F. Di Gennaro, D. Pizzo, C. Marotta, M. Antunes, V. Racalbuto, N. Veronese and L. Smith, *Int. J. Environ. Res. Public Health*, 2020, **17**, 2690.
2 H. A. Rothan and S. N. Byrareddy, *J. Autoimmun*., 2020, **109**, 102433.
3 X. Wu, K. Yu, Y. Wang, W. Xu, H. Ma, Y. Hou, Y. Li, B. Cai, L. Zhu, M. Zhang, X. Hu, J. Gao, Y. Wang, H. Qin, W. Wang, M. Zhao, X. Wu, Y. Zhang, L. Li, K. Li, Z. Du, B. W. J. Mol and B. Yang, *Engineering*, 2020, **6**, 1185.
4 A. Pawełczyk and L. Zaprutko, *Future Med. Chem*., 2020, **12**, 1743.
5 F. N. Novikov, V. S. Stroylov, I. V. Svitanko and V. E. Nebolsin, *Russ. Chem. Rev*., 2020, **89**, 858.
6 V. S. Stroylov and I. V. Svitanko, *Mendeleev Commun*., 2020, **30**, 419.
7 B. J. Langford, M. So, S. Raybardhan, V. Leung, D. Westwood, D. R. MacFadden, J.-P. R. Soucy and N. Daneman, *Clin. Microbiol. Infect*., 2020, **26**, 1622.
8 *Global Tuberculosis Report 2019*, WHO Report Reveals, WHO Media Centre, 2019, https://www.who.int/tb/publications/global_report/en.
9 V. Makarov, E. Salina, R. C. Reynolds, P. P. K. Zin and S. Ekins, *J. Med. Chem*., 2020, **63**, 8917.
10 M. Vass, K. Hruska and M. Franek, *Vet. Med*., 2008, **53**, 469.
11 A. M. Ginsberg, M. W. Laurenzi, D. J. Rouse, K. D. Whitney and M. K. Spigelman, *Antimicrob. Agents Chemother.*, 2009, **53**, 3720.
12 M. Matsumoto, H. Hashizume, T. Tomishige, M. Kawasaki, H. Tsubouchi, H. Sasaki, Y. Shimokawa and M. Komatsu, *PLoS Med.*, 2006, **3**, e466.
13 P. Kim, L. Zhang, U. H. Manjunatha, R. Singh, S. Patel, J. Jiricek, T. H. Keller, H. I. Boshoff, C. E. Barry III and C. S. Dowd, *J. Med. Chem.*, 2009, **52**, 1317.
14 E. V. Verbitskiy, S. A. Baskakova, N. A. Gerasimova, N. P. Evstigneeva, N. V. Zil'berberg, N. V. Kungurov, M. A. Kravchenko, G. L. Rusinov, O. N. Chupakhin and V. N. Charushin, *Mendeleev Commun*., 2018, **28**, 393.
15 E. V. Verbitskiy, E. M. Dinastiya, O. S. Eltsov, E. F. Zhilina, A. V. Schepochkin, G. L. Rusinov, O. N. Chupakhin and V. N. Charushin, *Mendeleev Commun*., 2020, **30**, 142.
16 N. Molchanova, J. E. Nielsen, K. B. Sørensen, B. K. Prabhala, P. R. Hansen, R. Lund, A. E. Barron and H. Jenssen, *Sci. Rep*., 2020, **10**, 14805.
17 N. K. Taneja and J. S. Tyagi, *J. Antimicrob. Chemother*., 2007, **60**, 288.
18 E. V. Verbitskiy, G. L. Rusinov, V. N. Charushin and O. N. Chupakhin, *Russ. Chem. Bull., Int. Ed*., 2019, **68**, 2172 (*Izv. Akad. Nauk, Ser. Khim*., 2019, 2172).
19 V. Sharma, N. Chitranshi and A. K. Agarwal, *Int. J. Med. Chem*., 2014, 202784.

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