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Green chemical principles based regioselective functionalization of 2,4,6-trichloropyrimidine-5-carbaldehyde: Application in the synthesis of new pyrimidines and pyrrolopyrimidine

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Abstract: The present work reports the synthesis of three new nitrogen-containing heteronuclear molecules (two pyrimidines and one pyrrolopyrimidine). Based on the 12 principles of green chemistry, chemical methodologies are planned and executed. Various phase transfer catalysts were examined in the crucial step to execute C–N bond formation (through the SnAr mechanism), TBAI was found to be a better option than those of TBAB and CTAB. The one-pot synthetic methodology was optimized involving Wittig olefination and bromination to achieve a key precursor for the synthesis of a new pyrrolopyrimidine.

Keywords: twelve principles of green chemistry; phase transfer catalysis; one-pot synthesis; Wittig olefination; synthesis of new *N*-heterocyclic compounds; halogen solvent-free processes; catalytic reactions.

INTRODUCTION

In the DNA and RNA structures, pyrimidine is a common structural motif present in the form of different nucleobases, such as cytosine, thymine and uracil. Scaffolds containing tetra substituted pyrimidines occupy a prominent position based on their biological applications.^{1–10} Recently, 2,4,6-trichloro-pyrimidine-5-carbaldehydes having cholesterol moiety are used for gelation.¹¹ Interest in the studies based on the derivatives of pyrrolo[2,3-*d*]pyrimidines has increased significantly after the introduction of nucleoside antibiotics, such as tubercidin, toyocamycin and sangivamycin.¹² In addition these tetra substituted pyrimidines are acting as precursors in the synthesise of new biologically active pyrrolo[2,3-

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-*d*]pyrimidines. A few representative pyrimidines and pyrrolo[2,3-*d*]pyrimidine structural motifs containing examples are shown in Fig. 1.

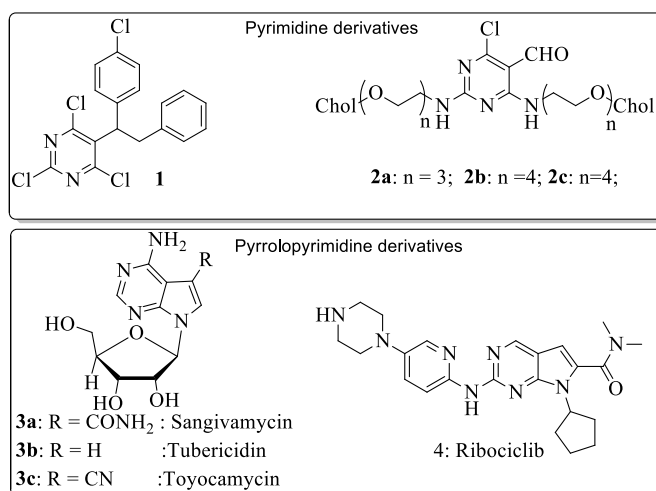


Fig. 1. Representative examples of pyrimidine and pyrrolopyrimidine derivatives.

EXPERIMENTAL

General procedures

All reactions were performed under a nitrogen atmosphere using anhydrous techniques unless otherwise stated. All commercially available materials and solvents were used directly without further purification. ¹H-NMR (400 MHz) and ¹³C-NMR (100 MHz) were recorded on a Bruker Avance NMR spectrometer using TMS as the internal standard in CDCl₃ or DMSO-*d*₆ solution. The mass spectra were determined on a THERMO LTQ (ESI) or Agilent 5973 MSD (EI) spectrometer. The IR spectra were recorded on Perkin-Elmer model 683 or 1310 spectrometers with sodium chloride optics or KBr pellets. All reactions were monitored by thin-layer chromatography (TLC) employing 0.25 mm Merck silica gel plates (60F-254). Column chromatography was performed using Acme silica gel (60–120 mesh). Visualization of the spots on the TLC plates was achieved either by exposure to UV light, and iodine vapor or by dipping the plates in phosphomolybdic acid–ceric (IV) sulfate–sulfuric acid solution (PMA solution) and heating the plates at 120 °C. All the products were purified by column chromatography. The structures were characterized by analysis of spectra data, namely ¹H-NMR, ¹³C-NMR, IR and mass spectra.

Analytical and spectral data are given in Supplementary material to this paper.

2,4-Dichloro-6-(cyclopentylamino)pyrimidine-5-carbaldehyde (7). To a stirred solution of 2,4,6-trichloro-pyrimidine-5-carbaldehyde **5** (5.0 g, 23.6 mmol) in a mixture of toluene (10 ml) and water (40 ml) was added cyclopentyl amine **6** (2.01 g, 23.6 mmol), CsCO₃ (4.0 g, 40 mmol) and a catalytic amount of TBAB (0.35 g, 1.08 mmol) at 25 to 35 °C. The reaction mass was maintained for 2–3 h at 25 to 35 °C. The organic layer was separated from the aqueous layer, washed with brine solution and dried over anhydrous Na₂SO₄. The organic layer was concentrated under vacuum to give a thick oily residue that was purified by column chromatography to give **7** (5.53 g, 90 %).

Methyl (Z)-2-bromo-3-(2,4-dichloro-6-(cyclopentylamino)pyrimidin-5-yl)acrylate (9). To a stirred solution of (methoxycarbonyl methyl)triphenylphosphoniumbromide, **8** (15.8 g, 38.0 mmol) in a mixture of dioxane (9 ml) and water (45 ml) was added *N*-bromosuccinamide (7.5 g, 42.1 mmol) at 0–5 °C. The mixture was stirred at 0–5 °C for 45 to 60 min. The temperature of the reaction mass was raised to 25 °C and then compound **7** (9.0 g, 34.5 mmol) was added followed by CsCO₃ (14.83 g, 46.01 mmol). After keeping the reaction mass at 25 °C for 2 to 3 h. it was dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure to obtain a yellow crude oil. The crude residue was purified by column chromatography to give **9** (12.29 g, 85 %)

*Methyl 2,4-dichloro-7-cyclopentyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (10)*. To a stirred solution of compound **9** (4.0 g, 10.1 mmol), K₂CO₃ (7.0 g, 50.6 mmol) and DABCO (0.56 g, 5.06 mmol) in 1,4 dioxane (20 ml) was added CuI (0.385 g, 2.02 mmol) under a nitrogen atmosphere at 25 °C. The temperature of the reaction mass was raised to reflux and maintained for 16.0 h under a nitrogen atmosphere. Then reaction mass was filtered and the filtrate washed with dioxane (4 ml). The filtrate was dried over anhydrous Na₂SO₄ and then concentrated to obtain a thick yellow syrup. Using columns chromatographic technique. The product **10** was purified by column chromatography (2.92 g, 90 %)

RESULTS AND DISCUSSION

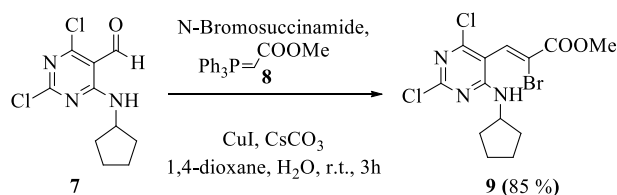
Synthesis of pyrimidine and pyrrolopyrimidine

The synthesis of new and diversified pyrrolopyrimidines using pyrimidine precursors was unexplored to date. Thus, it was intend to synthesize a series of N-heterocyclic compounds having a pyrimidine moiety as a common structural entity and to prepare new pyrrolo[2,3-*d*]pyrimidines based on the execution of green chemical approaches. In continuation of the execution of green chemical methodologies based on twelve principles of chemistry, in the current work, these advanced methodologies were extended to the synthesize N-heterocyclic compounds.^{13–18} The importance of one pot synthetic methodology is increasing in a fast manner.^{19–21} Extending new synthetic methodologies to the synthesis of a series of pyrimidine analogues and their characterization were the main objectives of this work. For this purpose, the synthesis a common intermediate having functionalizable groups on each carbon of pyrimidine was envisaged. The envisaged synthetic strategy involved the usage of reliable and high yield producing reactions such as C–N bond formation (through the S_NAr mechanism), the Wittig reaction and cyclization. To generate new and different analogs having pyrimidine moiety, compound 2,4,6-trichloropyrimidine-5-carbaldehyde was chosen which is having four functionalizable sites, *i.e.*, three chloro substituents and one aldehyde functionality. Compound **5** can be synthesized using barbituric acid as the starting material since it is a cheap commercially available material. The synthesis was initiated with barbituric acid that was converted into **5** using POCl₃ in DMF (Vilsmeier–Haack reaction conditions), the required pyrimidine derivative having four functionalizable groups was synthesized in 85 % yield (Scheme 1).²²

chromatogram with dichloro mass pattern in positive scan mode. The spectral data of **7** was in full agreement with the assigned structure.

TABLE I. Optimization of the S_NAr reaction; equivalence of base and PTC were calculated concerning the equivalence of substrates **2** and **3**

S. No.	PTC (4.5 mol. %, equivalence)	Base (1.7 equivalence)	Isolated yield, % (equivalence)
1	TBAI	K ₂ CO ₃	80
2	TBAI	KHCO ₃	65
3	TBAI	Na ₂ CO ₃	75
4	TBAI	CsCO ₃	70
5	TBAB	CsCO₃	90
6	TBAB	KHCO ₃	80
7	TBAB	Na ₂ CO ₃	70
8	TBAB	NaHCO ₃	50
9	CTAB	K ₂ CO ₃	60
10	CTAB	KHCO ₃	50
11	CTAB	Na ₂ CO ₃	60
12	CTAB	CsCO ₃	50



Scheme 2. One pot Wittig and bromination reaction.

Although one-pot bromination and Wittig reactions were optimized previously with simple substrates such as aliphatic, and aromatic compounds most of the reactions used organic solvents such as DCM or DMSO only.²⁴ The main drawback in those reaction conditions was the non-aqueous media. To implement green chemical methodology by using an aqueous solvent along with increasing the yield of the product, the reaction conditions in the aqueous media containing a biphasic system were optimized. In this way, the usage of organic solvents was reduced by employing an eco-friendly aqueous solvent. Wittig olefination of compound **7** using **8** and Na₂CO₃ at 25 °C resulted in olefin **9** in 65 % yield. For improving the yield of the conversion of **7** into **8**, each parameter of the reaction was systematically examined (as shown in Table II). From Table II, it is very clear that the availability of K₂CO₃ to the reactants was greater in a bi-phasic mixture of 1,4-dioxane + water, which made the reaction faster with more complete transformation of **7** into **8** and higher yields (Scheme 2). After completion of the reaction, MTBE was used in the purification step, for extraction purposes,

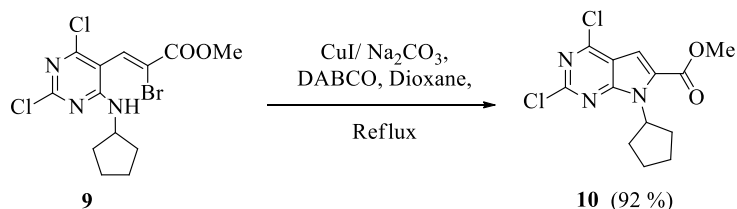
TPP oxide by-products can be removed selectively from the reaction mixture and in this way the usage of a hazardous organic solvent was reduced to some extent.

TABLE II. Optimization of the Wittig reaction

S. No.	Solvent	Base	Reaction temperature, °C	Reaction time, h	Isolated yield, %
1	CH ₂ Cl ₂	K ₂ CO ₃	-20	> 48	~35
2	Benzene	K ₂ CO ₃	-20	> 48	~ 40
3	Methanol	Na ₂ CO ₃	-20	> 48	~ 45
4	Toluene + methanol	Na ₂ CO ₃	-20	> 48	~ 40
5	1,4-Dioxane	Na ₂ CO ₃	-20	7	50
6	1,4-Dioxane	Na ₂ CO ₃	0	5	55
7	1,4-Dioxane + water	Na ₂ CO ₃	-20	3	80
8	1,4-Dioxane + water	Na ₂ CO ₃	0	2	85
9	1,4-Dioxane + water	CsCO₃	25	1	85

Compound **9** was analyzed using ¹H-NMR by the appearance of the cyclopentyl amine structure representing protons signals ranging from δ 1.5 to 4.5 ppm, the NH proton was observed at 7.45 ppm and this peak was absent in the D₂O exchanged ¹H-NMR spectrum. In addition, compound **9** was confirmed by the appearance of its mass peaks at m/z 394 and 396 over mass chromatogram with bromo and dichloro mass pattern in positive scan mode. The spectral data of **9** was in full agreement with the assigned structure.

Compound **9** was converted to **10** using copper iodide, Na₂CO₃ and DABCO in 1,4-dioxane with a 92 % yield (Scheme 3).²⁵ As shown in Table III, the best conversion of the reaction from **9** to **10** was achieved with Na₂CO₃ in 1,4-dioxane at 110 °C. It was observed that inorganic bases were more effective in obtaining better cyclization conditions than the organic base diisopropylethylamine (DIPEA).²⁶ After finalizing the conversion, compound **10** was purified using column chromatography. Compound **10** was characterized based on ¹H-NMR by the appearance of proton signal of the cyclized five-membered ring alkene at δ 7.4 ppm, in addition to the appearance of its mass peaks at m/z 314 over mass chromatogram with a dichloro mass pattern in positive scan mode. The spectral data of **10** was in full agreement with the assigned structure.



Scheme 3. Cyclization reaction.

TABLE III. Optimization of the cyclization reaction

S. No.	Solvent	Base	Temperature, °C	Reaction time, h	Isolated yield, %
1	Dichloromethane	K ₂ CO ₃	35	No reaction	-
2	Tetrahydrofuran	K ₂ CO ₃	65	> 36	30
3	Toluene	K ₂ CO ₃	110	> 36	60
4	Toluene	Na ₂ CO ₃	110	> 36	60
5	Toluene	KO ^t Bu	110	> 36	25
6	1,4-dioxane	Et ₃ N	110	> 36	25
7	1,4-dioxane	DIPEA	110	> 36	20
8	1,4-dioxane	Na₂CO₃	110	12	92

CONCLUSIONS

The outstanding features of this synthetic methodology are: *i*) two aqueous phase transformations such as C–N bond formation and Wittig reaction, *ii*) one pot synthetic methodology that includes both Wittig reaction and bromination, *iii*) one phase transfer catalytic reaction using TBAB in C–N bond formation reaction, *iv*) all reactions are carried out by catalysts such as TBAB and CuI as two-room temperature reactions and *v*) all reactions and procedures are halogen solvent free processes.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: <https://www.shd-pub.org.rs/index.php/JSCS/article/view/11028>, or from the corresponding author on request.

ИЗВОД

РЕГИОСЕЛЕКТИВНА ФУНКЦИОНАЛИЗАЦИЈА 2,4,6-ТРИХЛОРПИРИМИДИН-5-КАРБ-АЛДЕХИДА НА АПРИНЦИПИМА ЗЕЛЕНЕ ХЕМИЈЕ: ПРИМЕНА У СИНТЕЗИ НОВИХ ПИРИМИДИНА И ПИРОЛОПИМИДИНА

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У овом раду приказана је синтеза три нова хетероциклична једињења азота (два деривата пиримидина и један дериват пиролопиримидина). План хемијске методологије синтезе је заснован на 12 принципа зелене хемије и план је реализован. Испитани су различити катализатори преноса између фаза у најважнијем реакционом кораку, формирања C–N везе (S_NAr механизмом) и утврђено је да је најбољи резултат постигнут коришћењем ТВАИ у поређењу са ТВАВ и СТАВ. Оптимизована је нова синтетичка методологија која укључује Витихову (Wittig) олефинацију и бромовање за добијање најважнијег прекурсора у синтези нових пиролпиримидина.

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REFERENCES

1. P. K. Maji, *Curr. Org. Chem* **24** (2020) 1055 (<https://doi.org/10.2174/1385272824999200507123843>)
2. A. Mahapatra, T. Prasad, T. Sharma, *Futur. J. Pharm. Sci.* **7** (2021) 1 (<https://doi.org/10.1186/s43094-021-00274-8>)
3. H. K. Akula, H. Kokatla, G. Andrei, R. Snoeck, D. Schols, J. Balzarini, L. Yang, M. K. Lakshman, *Org. Biomol. Chem.* **15** (2017) 1130 (<https://doi.org/10.1039/C6OB02334G>)
4. S. Kumar, B. Narasimhan, *Chem. Central J.* **12** (2018) 38 (<https://doi.org/10.1186/s13065-018-0406-5>)
5. A. Frank, F. Meza-Arriagada, C. O. Salas, C. Espinosa-Bustos, H. Stark, *Bioorg. Med. Chem.* **27** (2019) 3194 (<https://doi.org/10.1016/j.bmc.2019.05.042>)
6. A. Ali, M. Khalid, M. F. U Rehman, S. Haq, A. Ali, M. N. Tahir, M. Ashfaq, F. Rasool, A. C. Braga, *ACS Omega* **5** (2020) 15115 (<https://doi.org/10.1021/acsomega.0c00975>)
7. A. Ali, M. Khalid, M. N. Tahir, M. Imran, M. Ashfaq, R. Hussain, M. A. Assiri, I. Khan, *ACS Omega* **6** (2021) 7047 (<https://doi.org/10.1021/acsomega.0c06323>)
8. A. Ali, A. Kuznetsov, M. Ashfaq, M. N. Tahir, M. Khalid, M. Imran, A. Irfan, *J. Mol. Struct.* **1243** (2021) 130789 (<https://doi.org/10.1016/j.molstruc.2021.130789>)
9. M. Khalid, A. Ali, S. Haq, M. N. Tahir, J. Iqbal, A. A. C. Braga, M. Ashfaq, S. U. H. Akhtar, *J. Mol. Struct.* **1224** (2021) 129308 (<https://doi.org/10.1016/j.molstruc.2020.129308>)
10. M. Ashfaq, A. Ali, A. Kuznetsov, M. N. Tahir, M. Khalid, *J. Mol. Struct.* **1228**(2021) 129445 (<https://doi.org/10.1016/j.molstruc.2020.129445>)
11. S. Datta, S. Bhattacharya, *Soft Matter.* **11** (2015) 1945 (<https://doi.org/10.1039/C4SM02792B>)
12. P. K. Gu, S. Daunert, M. R. Nassiri, L. L. Wotring, J. C. Drach, L. B. Townsend, *J. Med. Chem.* **32**(1989) 402 (<https://doi.org/10.1021/jm00122a019>)
13. D. S. Ramakrishna, *Chem. Data Collect.* **33** (2021) 100685 (<https://doi.org/10.1016/j.cdc.2021.100685>)
14. D. S. Ramakrishna, *Chem. Data Collect.* **32** (2021) 100667 (<https://doi.org/10.1016/j.cdc.2021.100667>).
15. D. S. Ramakrishna, A. Pradhan, *ARKIVOC* **2021** (2021) 1 (<https://doi.org/10.24820/ark.5550190.p011.519>)
16. G. Kumaraswamy, D. Ramakrishna, K. Santhakumar, *Tetrahedron: Asymmetry* **21** (2010) 544 (<https://doi.org/10.1016/j.tetasy.2010.02.024>)
17. G. Kumaraswamy, K. Sadaiah, D. S. Ramakrishna, N. Police, B. Sridhar, J. Bharatam, *Chem. Commun.* (2008) 5324 (<https://doi.org/10.1039/B810770J>)
18. G. Kumaraswamy, A. Pitchaiah, G. Ramakrishna, D. S. Ramakrishna, K. Sadaiah, *Tetrahedron Lett.* **47** (2006) 2013 (<https://doi.org/10.1016/j.tetlet.2006.01.050>)
19. H. P. Kokatla, M. K. Lakshman, *Org. Lett.* **20** (2010) 4478 (<https://doi.org/10.1021/ol101655h>)
20. R. Meesala, Y. K. Lee, A. S. Md. I. Abdullah, Md. N. Mordi, N. A. Rahman, *Synlett* **31** (2020) 2054 (DOI: 10.1055/s-0040-1706477)
21. R. Meesala, A. S. Md. Arshad, Md. N. Mordi, S. M. Mansor, *Tetrahedron* **72** (2016) 8537 (<https://doi.org/10.1016/j.tet.2016.10.069>)
22. J. M. Hatcher, J. Zhang, H. G. Choi, G. Ito, D. R. Alessi, N. S. Gray, *ACS Med. Chem. Lett.* **6** (2015) 584 (<https://doi.org/10.1021/acsmchemlett.5b00064>)
23. R. L. Beingessner, B. L. Deng, P. E. Fanwick, H. Fenniri, *J. Org. Chem.* **73** (2008) 931 (<https://doi.org/10.1021/jo7021422>)

24. U. Karama, R. Mahfouz, Z. Al-Othman, I. Warad, A. Almansour, *Synth. Comm.* **43** (2013) 893 (<https://doi.org/10.1080/00397911.2011.614712>)
25. Y. H. Jang, S. W. Youn, *Org. Lett.* **16** (2014) 3720 (<https://doi.org/10.1021/o15015398>)
26. A. Udayasri, M. M. Chandrasekhar, M. V. N. Brahmeswararao, G. Varanasi, P. L. Praveen, D. S. Ramakrishna, *TopCatal.* (2022) (<https://doi.org/10.1007/s11244-022-01602-9>).

