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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 synthesize 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.

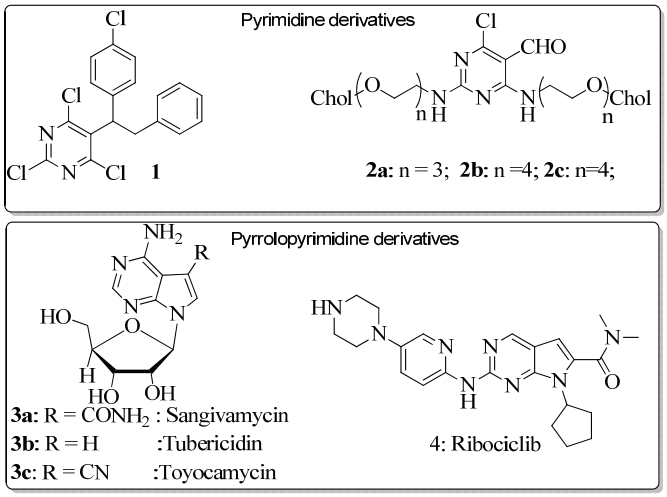


Fig. 1. Representative examples of pyrimidine and pyrrolopyrimidine derivatives.

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. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) were recorded on a Bruker Avance NMR spectrometer using TMS as the internal standard in $CDCl_3$ 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 ^{1}H-NMR, ^{13}C-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), $CsCO_3$ (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 Na_2SO_4. 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 %).

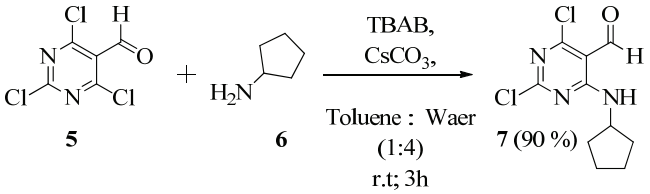
*Methyl (Z)-2-bromo-3-(2,4-dichloro-6-(cyclopentylamino)pyrimidin-5-yl)acrylate (**9**)*. To a stirred solution of (methoxycarbonyl methyl)triphenylphosphoniumbromide, **8** (15.8 g, 38.0 mmol) in a mixture of dioxane (9 ml) and water (45 ml) was added *N*-bromosuccinamide (7.5 g, 42.1 mmol) at 0–5 °C. 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 $CsCO_3$ (14.83 g, 46.01 mmol). After keeping the reaction mass at 25 °C for 2 to 3 h. it was dried over anhydrous Na_2SO_4 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), K_2CO_3 (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 Na_2SO_4 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 $POCl_3$ in DMF (Vilsmeier–Haack reaction conditions), the required pyrimidine derivative having four functionalizable groups was synthesized in 85 % yield (Scheme 1).[22]



Scheme 1. C–N bond formation reaction.

After obtaining the required intermediate, functionalization of the 2nd/6th position was explored using cyclopentyl amine to generate a new C–N bond. The main difficulty involved in this reaction is that there may be a chance of the formation of imine product using aldehyde and amine through condensation reaction (a parallel reaction) instead of a C–N bond formation reaction.

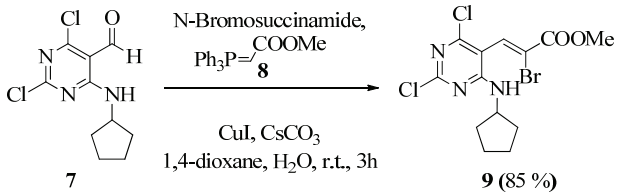
A similar reaction with this substrate **5** using toluene solvent was reported.[23] Though toluene is a preferable solvent in synthetic organic chemistry in comparison with other organic solvents, such as chlorinated solvents (DCM, CCl_4) or benzene, it still has some negative impacts on nature. The usage of organic solvents should be reduced to a bare minimum by employing/increasing ecofriendly solvents, such as water, to carry out the reaction. This reaction was optimized with the higher solvent contribution of water (80 %) as the major solvent in comparison with that of toluene (20 %) solvent as the minor solvent. The other advantage of using higher amounts of water is to diminish the formation of imine products that could be obtained from aldehyde and amine. Water was not only a solvent but also a byproduct in this parallel imine condensation reaction. Hence, the Lechleiter principle was applied, *i.e.*, by increasing the concentration of water, the formation of imine product can be reduced. The role of water in this reaction is not only to decrease the usage of the toluene solvent but also to lessen the production of imine product. The reaction was optimized based on the following parameters shown in Table I. Different phase transfer catalysts were examined, such as TBAB, TBAI and CTAB. Different bases, such as K_2CO_3, $KHCO_3$, Na_2CO_3, $NaHCO_3$ and $CsCO_3$, were employed to obtain higher yields of the required product in various solvent combinations. Based on careful experimentation of the reaction under various conditions (Table I), a higher yield of the product was obtained using $CsCO_3$ as the base, TBAB as PTC, and solvents ratio toluene:water of 1:4. The required product was obtained in good yield using TBAB in comparison with other phase transfer catalysts (Scheme 1).

Compound **7** was characterized based on its ^{1}H-NMR spectrum, the appearance of cyclopentyl amine structure representing protons signals ranging from δ 1.5 to 4.5 ppm, the NH proton was observed at δ 9.30 ppm and this peak was absent in its D_2O exchanged ^{1}H-NMR spectrum. In addition compound **7** was confirmed by the appearance of its mass peak at *m*/*z* 260.0 (M+1) over mass

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_2CO_3	80
2	TBAI	$KHCO_3$	65
3	TBAI	Na_2CO_3	75
4	TBAI	$CsCO_3$	70
5	**TBAB**	**$CsCO_3$**	**90**
6	TBAB	$KHCO_3$	80
7	TBAB	Na_2CO_3	70
8	TBAB	$NaHCO_3$	50
9	CTAB	K_2CO_3	60
10	CTAB	$KHCO_3$	50
11	CTAB	Na_2CO_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 Na_2CO_3 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 K_2CO_3 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,

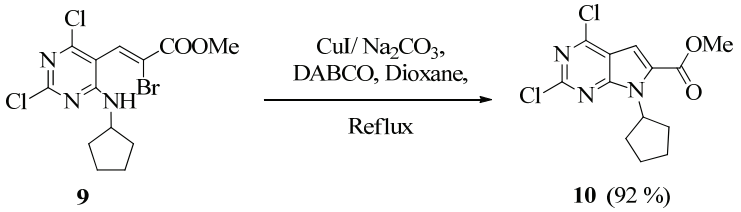
TPP oxide by-products can be removed selectively from the reaction mixture and in this way the usage of a hazardous organic solvent was reduced to some extent.

TABLE II. Optimization of the Wittig reaction

S. No.	Solvent	Base	Reaction temperature, °C	Reaction time, h	Isolated yield, %
1	CH_2Cl_2	K_2CO_3	–20	> 48	~35
2	Benzene	K_2CO_3	–20	> 48	~ 40
3	Methanol	Na_2CO_3	–20	> 48	~ 45
4	Toluene + methanol	Na_2CO_3	–20	> 48	~ 40
5	1,4-Dioxane	Na_2CO_3	–20	7	50
6	1,4-Dioxane	Na_2CO_3	0	5	55
7	1,4-Dioxane + water	Na_2CO_3	–20	3	80
8	1,4-Dioxane + water	Na_2CO_3	0	2	85
9	1,4-Dioxane + water	$CsCO_3$	25	1	85

Compound **9** was analyzed using ^{1}H-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 D_2O exchanged ^{1}H-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, Na_2CO_3 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 Na_2CO_3 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 ^{1}H-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.



9 **10** (92 %)

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_2CO_3	35	No reaction	-
2	Tetrahydrofuran	K_2CO_3	65	> 36	30
3	Toluene	K_2CO_3	110	> 36	60
4	Toluene	Na_2CO_3	110	> 36	60
5	Toluene	KO^tBu	110	> 36	25
6	1,4-dioxane	Et_3N	110	> 36	25
7	1,4-dioxane	DIPEA	110	> 36	20
8	1,4-dioxane	Na_2CO_3	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-КАРБАЛДЕХИДА НА АПРИНЦИПИМА ЗЕЛЕНЕ ХЕМИЈЕ: ПРИМЕНА У СИНТЕЗИ НОВИХ ПИРИМИДИНА И ПИРОЛОПИМИДИНА

ALLU UDAYASRI[1], MANCHIKANTI M. CHANDRASEKHAR[1], BRAHMESWARARAO M. V. NAGA[2], GANESH VARANASI[2] и DUGGIRALA S. RAMAKRISHNA[1]

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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 TBAI у поређењу са TBAB и CTAB. Оптимизована је нова ситетичка методологија која укључује Витихову (Wittig) олефинацију и бромовање за добијање најважнијег прекурсора у синтези нових пиролпиримидина.

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