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Green Synthesis of Biologically Active Pyrazolopyrimidine Derivatives Using an Ionic liquid 2-Methyl-3-butylimidazolium chloride

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Abstract: Pyrazolopyrimidine derivatives have received a great deal of attention due to their pharmacological activities. Avoiding the use of organic solvents in synthesis is a paradigm shift directed at developing more benign chemistry, and with ionic liquids surprisingly can lead to access to new compounds**.** The application of ionic liquids in organic synthesis also provides chemical processes with special emphases such as enhanced reaction rates, absence of highly inflammable solvents, higher yields of pure products, better selectivity, reusability of the ionic liquid catalyst, rapid optimization of reactions in parallel and several eco-friendly advantages. An efficient and environmental benign method is reported for the synthesis of some Pyrazolopyrimidine derivatives using 3-methyl-1-phenyl-5-pyrazolone with carbonyl compounds in ionic liquid 2-methyl-3-butyl imidazolium chloride. It is noteworthy to mention that this method of synthesis requires less time, less temperature, better yield and less amount of by-products than conventional reactions. The recyclability and reusability of the catalyst have been tested. The structures of all the synthesized Pyrazolopyrimidine derivatives have been established on the basis of elemental and spectral analysis. The compounds have been screened for their antimicrobial activity against various micro-organisms. All the compounds showed moderate to good activity against different micro-organisms at 256µg/ml.

Keywords: Green synthesis, ionic liquid, pyrazolopyrimidine derivatives, spectral analysis.

Introduction and Experimental

The derivatives of pyrazolone are important class of antipyretic and analgesic compounds[1]. 1-Phenyl-3-methyl-4-arylmethylene-5-pyrazolones are very useful intermediates in the synthesis of substituted pyrazolones, generally, which were prepared by the condensation of 3-methyl-1-phenyl-5-pyrazolone with aromatic aldehydes[2]. Pyrazolopyrimidine derivatives have received a great deal of attention due to their pharmacological activity[3], such as allopurinol[4], which is still the drug of choice for the treatment of hyperurecemia and gouty arthritis[5]. Pyrazolopyrimidine are purine analogues and as such they have useful properties as antimetabolites in purine biochemical reaction[6]. Moreover, these compounds also display marked antitumor and antileukemic activity[7]. Pyrazolopyrimidine derivatives have demonstrated promising antimicrobial activity against Gram-positive bacteria[8]. Synthesis of such biologically important compounds assumes great importance. Recently, some new methods such as microwave irradiation[9], supported solid catalyst[10], solid state reactions etc.[11] have been applied to facilitate this reaction. However, some of these methods are limited due to slow reaction rate, low yields, side products, tedious workup, and the use of toxic solvents or

expensive catalysts [12, 13].
In recent years, the interest in room temperature ionic liquids is increasing as green reaction media for synthetic organic chemistry[14]. It is worth to note that Shingare et al. reported the Knoevenagel condensation reactions in ionic liquids ethyl ammonium nitrate of pyrazolone with few aromatic aldehydes gave moderate to high yields[15]. In continuation of our interest in using ionic liquids as a green reaction medium for the synthesis pyrazolone pyrimidine derivatives using 3-methyl-1-phenyl-5-pyrazolone with urea and various substituted aldehydes in the presence of 2-methyl-3-butyl imidazolium chloride as catalyst.

Materials and reagents

All the chemicals were of AR grade and used without further purification unless otherwise stated. All the aromatic aldehydes were obtained from S.D. fine chemicals, Mumbai. Ionic liquid was obtained from Aldrich chemicals, USA and used as received.

Analytical and spectral methods

Melting points of all the compounds were determined in open capillaries and are uncorrected. The homogeneity of compounds was checked by TLC on silica gel 'G' coated glass plates. IR spectra were recorded in KBr on Shimadzu FT-IR 8300 spectrometer and ^{1}H NMR spectra were recorded in Varian 400 MHZ and Bruker Advance II instruments in $CDCl_3$ by using TMS as internal standard. Mass spectra of the synthesized compounds have been recorded on a Jeol SX 102/DA-6000 spectrometer.

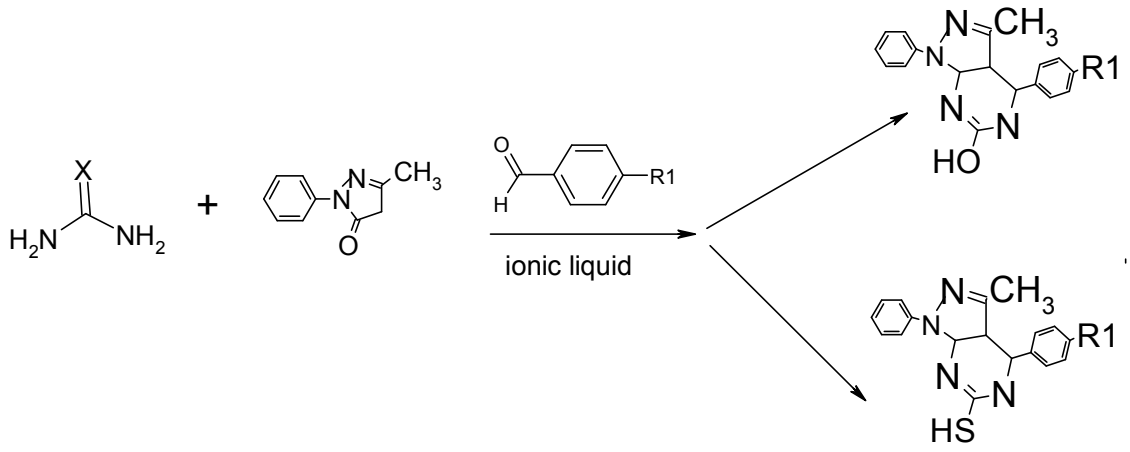
Synthesis of pyrazolone pyrimidine derivatives

3-methyl-1-phenyl-5-pyrazolone (0.01 moles), urea (0.01 moles) and various substituted aldehydes (0.01 moles) were added in 2-Methyl-3-butyl imidazolium chloride. The reaction mixture was refluxed for appropriate time; the reaction was monitored by thin liquid chromatography. Upon completion of the reaction the clear solution thus obtained was treated with crushed ice to give the solid product which was filtered and dried. The crude product was purified by recrystallization from absolute alcohol. The Ionic liquid in the reaction was recovered simply by drying in vacuum. The results were summarized in Table I.

Conventional method

The mixture of 3-methyl-1-phenyl-5-pyrazolone (0.01 moles), urea (0.01 moles) and various substituted aldehydes (0.01 moles) in ethanol was refluxed for 6 hours in water bath. The clear solution thus obtained was treated with crushed ice to give the solid product which was filtered and dried. The crude product was purified by recrystallization from absolute alcohol.

Scheme 1



X=O, S

1 2 3a-f (X=O) and 4a-f (X =S)

Table 1. Results of the synthesis of several pyrazolone pyrimidine derivatives using urea

Compound[a]	-R_1	m.p.(°C)	Present method		Conventional method	
			Yield (%)	Time (min)	Yield (%)	Time (min)
3a	-4-NO_2	183	90[b]	60	71	180
3b	-4-NO_2	183	92[c]	60	71	180
3c	-4-NO_2	183	78[d]	60	67	180
3d	-4-NO_2	183	75[e]	60	70	180
3e	-4-OMe	252	88	90	74	180
3f	-4-Cl	154	93	90	69	180
3g	-2-OH	166	89	75	67	180
3h	-H	185	87	80	70	180
3i	-4-F	124	86	85	65	180

[a]all reaction were run with 3-methyl-1-phenyl-5-pyrazolone (0.01mole), carbonyl compound (0.01mole) and urea (0.01mole) in ethanol
[b] second run use of 2-methyl -3- butyl imidazolium chloride
[c] third run use of 2-methyl -3- butyl imidazolium chloride
[d] reaction was run in THF
[e] reaction was run in DMF

Table 2. Results of the synthesis of several pyrazolone pyrimidine derivatives using thiourea

Compound[a]	-R1	m.p.(°C)	Present method		Conventional method	
			Yield (%)	Time(min)	Yield(%)	Time (min)
4a	-4-NO_2	224	90[b]	60	74	180
4b	-4-NO_2	224	94[c]	60	73	180
4c	-4-NO_2	224	80[d]	60	69	180
4d	-4-NO_2	224	85[e]	60	70	180
4e	-4-OMe	285	88	90	77	180
4f	-4-Cl	181	95	90	72	180
4g	-2-OH	180	90	75	67	180
4h	-H	186	87	80	70	180
4i	-4-F	151	86	85	65	180

[a] all reaction were run with 3-methyl-1-phenyl-5-pyrazolone (0.01mole), carbonyl compound (0.01mole) and thiourea (0.01mole) in ethanol
[b] second run use of 2-methyl -3- butyl imidazolium chloride
[c] third run use of 2-methyl -3- butyl imidazolium chloride
[d] reaction was run in THF
[e] reaction was run in DMF

Table 3. Spectral and elemental analyses of a few representative products

Entry	Product	IR (KBr) cm^{-1}	^{1}H NMR ($CDCl_3$) ppm	EIMS m/z
1	3e	3504,3421,3002,1635,1576.	δ9.07(1H,s),4.86(s,1H),3.70(s,3H),2.0-2.04(m,20H) 2.46(s,3H),6.85-8.70 (m,8H).	594(M+)
2	3h	3506,3422,3005,1632,1572.	δ8.50(s,1H),4.87(s,1H),3.70-3.74(m,8H),2.14-2.35(m,8H),2.46 (s,3H),7.17-7.90 (m,9H).	568(M+)
3	4e	2550, 3422, 3001, 1633, 1573.	δ9.12,1.19(s,1H),3.70(s,3H),3.37-3.78(m,8H) 2.0-2.70(m,8H),3.82(s,3H),2.50(s,3H),6.73-8.04 (m,8H).	614(M+)
4	4h	2558,3425,3005,1637,1574,660.	δ8.50(s,1H),1.25(m,1H),3.72-.74(m,8H),2.17-2.32(m,8H), 2.35(s,3H),7.16-7.91(m,9H)	584(M+)

Table 4. Results of antibacterial activity of compounds 3a,e-i

Compound	*Escherichia coli*		*Pseudomonas aeruginosa*		*Staphylococcus aureus*		*Bacillus subtilis*		*C.albicanes*	
	128µg/mL	256 µg/mL	128µg /mL	256 µg/mL	128µg /mL	256 µg/mL	128µg /mL	256 µg/mL	128µg /mL	256 µg/mL
3a	-	++	-	++	-	++	-	++	-	-
3e	-	+++	-	+++	-	+++	-	+++	-	-
3f	-	+++	-	+++	-	+++	-	+++	-	-
3g	-	+++	-	+++	-	+++	-	+++	-	-
3h	-	++	-	++	-	++	-	++	-	-
3i	-	++	-	++	-	++	-	++	-	-

(-) < 6mm, (+) =7-10mm, (++) =11-15mm, (+++) =16 -21mm, (++++) = 22-28mm

Table 5. Results of antibacterial activity of compounds 4a,e-i

Compound	*Escherichia coli*		*Pseudomonas aeruginosa*		*Staphylococcus aureus*		*Bacillus subtilis*		*C.albicanes*	
	128µg/mL	256 µg/mL	128µg /mL	256 µg/mL	128µg /mL	256 µg/mL	128µg /mL	256 µg/mL	128µg /mL	256 µg/mL
4a	-	++	-	++	-	++	-	++	-	-
4e	-	++	-	++	-	++	-	++	-	-
4f	-	+++	-	+++	-	+++	-	+++	-	-
4g	-	+++	-	+++	-	+++	-	+++	-	-
4h	-	++	-	++	-	++	-	++	-	-
4i	-	++	-	++	-	++	-	++	-	-

(-) < 6mm, (+) =7-10mm, (++) =11-15mm, (+++) =16 -21mm, (++++) = 22-28mm

Results and Discussion

The reaction was found to be general and applicable to aromatic aldehydes. All the tested aromatic aldehydes bearing various substituents such as chloro, nitro, methoxyl etc. could successfully react with 3-methyl-1-phenyl-5-pyrazolone within 90 minutes with high yields. The results are displayed in table 1.The examined ionic liquid 2-methyl-3-butyl imidazolium chloride was efficient and gave excellent results, which could truly be compared with classical molecular solvents with the advantage of rate acceleration and increase of yield. Interestingly we have not obtained the side products which were usually accompanied with the target compounds when the reaction was carried out in classic molecular solvents (3c, 3d). Moreover, the ionic liquid could be recovered and reused with no appreciable decrease in yields and reaction rates (compound 3a, 3b).

Antibacterial activity studies

Pyran and fused pyran derivatives have attracted a great deal of interest due to their association with various kids of biological properties. They have been reported for their antimicrobial [16,17,18,19], antiviral[20,21], anticonvulsant[22], cytotoxic[23],antigenotoxic[24] activities. The incorporation of another heterocyclic moiety in pyrans either in the form of a substituent or as a fused component changes its properties and converts it into an altogether new and important heterocyclic derivative. Pyrazoles have attracted particular interest over the last few decades due to the use of such ring system as the core nucleus in various drugs. They are well known for their popular pharmacological activities. Considering the importance of pyrazolone derivatives, it was thought worthwhile to synthesize new compounds incorporating both these moieties. All the compounds synthesized in the present study were screened for their antibacterial activity against some bacteria (both gram-negative and gram- positive) namely *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis and C.albicanes* by filter paper disc technique. The minimum inhibitory concentration (MIC) was ascertained by tube dilution method as per the standard procedures available in the literature. The results are presented in tables 4 and 5.It is understood from the screening data that compounds 3f-g and 4f-g showed highest degree of inhibition against bacteria namely *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus, Bacillus subtilis* at 256 µg/mL .While compounds 3a, h, i and 4a, h, i exhibited less inhibition activity against the aforementioned bacteria

at 256 µg/mL No significant inhibition activity was noticed against any bacteria at concentration 128 µg/mL It is interesting to note that no inhibition activity was observed with all the compounds synthesized in this study against the bacteria *C.albicanes* at both the concentration levels.

Conclusion

In conclusion, we have demonstrated the reaction between 3-methyl-1-phenyl-5-pyrazolone with aldehydes and urea/thiourea could be effectively performed in the ionic liquid 2-methyl-3-butyl imidazolium chloride. The present method has many obvious advantages over classical procedures, including being environmentally more benign, simple, the ease of product isolation, higher yield, shorter reaction times, and the potential for recycling ionic liquid and catalyst. The recyclability and reusability of the catalyst have been tested. The structures of all the synthesized Pyrazolopyrimidine derivatives have been established on the basis of elemental and spectral analysis. The compounds have been screened for their antimicrobial activity against various micro-organisms. All the compounds showed moderate to good activity against different micro-organisms at 256µg/ml.

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