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Synthesis of some uracil derivatives using ionic liquid

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ABSTRACT

In the present study, some 3-(substituted phenyl)-2, 10-dihydro-10-oxo-1-thioxo-1Hpyrimido[6, 1-b] quinazoline-4-carbonitriles were prepared from 6-(substituted phenyl)-1,2,3,4-tetrahydro-4-oxo-2-thioxopyrimidine-5 carbonitriles. The synthesis involved three steps. The first step was one pot condensation of thiourea with substituted benzaldehydes in alcohol using potassium carbonate as catalyst to give uracils (TSI –TSIV). These uracils were then converted to the compounds, 4-chloro-1, 2-dihydro-6-substituted phenyl-2-thioxopyrimidine-5-carbonitrile (TSIa-TSIVa) by overnight stirring of with $POCl_3$ using DMF as solvent. Later on the title compounds, quinazoline derivatives (T1-T4) were prepared in one step by reacting (TSIa-TSIVa) with anthranilic acid in DMSO using catalytic amount of ionic liquid (1-n-butylimidazolium chloride). The structures of newly synthesized compounds (T1-T4) have been confirmed on the basis of spectral data.

Keywords: Uracil, quinazoline, ionic liquid, one pot.

INTRODUCTION

The uracil is reported to possess various possess biological activities attributed to various modifications at the ring nitrogen's, N1 and N3 as well as modifications at position 2, 5 and 6 like enzyme inhibition[1],inhibition of DNA synthesis [2], antiretroviral[3-6], antineoplastic agents [7] as well as antimycobacterial[8-12].

Also, the quinazoline nucleus is reported to possess various biological activities from antimicrobial [13], antihypertensive [14] and anticancer [15] to name a few.

Ionic liquids (ILs) have attracted increasing interest recently in the context of green organic synthesis. Actual mechanism of IL as a catalyst is not exactly known [16].

From the literature it is found that IL are vastly used in Cyclocondensation type of reaction. Cyclocondensation is a kind of annulation reaction involving the formation of a ring from one or several acyclic precursors is a set of condensation reactions in which one-, two-, three-, or ulticomponent reactants yield a single main cyclic product with the accompanying formation of some other small molecule. Their use has been reported for synthesis of vast number of heterocycles as pyrimidines, furans, thiophenes, quinazolines, benzodiazepines, condensed pyrimidin-4 (3H) ones etc [17].

In continuation of our work in uracil derivatives [18], and with this all literature survey of IL, we decided to try the use of IL in our step for the synthesis of derivatives containing fused uracils and quinazolines by cyclocondensation reaction using 1-*n*-butylimidazolium chloride ($bbim^+Cl^-$) as ionic liquid.

MATERIALS AND METHODS

General

The reagents employed were of analytical grade. ^{1}H NMR spectra's were recorded on a Varian Mercury YH300 (300 MHz FT NMR) spectrophotometer using TMS as an internal reference (chemical shift represented in δ ppm). FTIR spectra of the synthesized compounds were recorded using KBr on a Jasco FTIR V 430 + spectrometer using Diffuse Reflectance Attachment and are reported in cm^{-1}.

Purity of the compounds was checked on 'Silica Gel G' coated on laboratory micro slides prepared by dipping method or precoated plates, eluent was the mixture of different polar and non-polar solvents in varying proportions and detection was done either by observing in UV light. The absence of TLC spots for starting materials and appearance of new TLC spot at different R_f value ensured the completion of reaction. The scientific microwave system, Catalyst System, Model CATA-R was used for preparation of uracils.

Method

The title compounds were prepared in the following steps:

STEP 1: General procedure for synthesis of 6-(4-substitutedphenyl)-1,2,3,4-tetrahydro-4-oxo-2-thioxopyrimidine-5-carbonitrile (TSI-TSIV) [18,19] **:**

Procedure: A mixture of thiourea 5.0g (0.065 mol), ethyl cyanoacetate 7.0 ml (0.065 mol; density=1.061), substituted benzaldehyde 6.8 ml (0.065 mol; density=1.18) and potassium carbonate (catalytic amount) was taken in about 30 ml of ethanol (one- pot reaction). The reaction mixture was subjected to microwave pulse for (450 w) for about 15 minutes. The completion of reaction was monitored by TLC, the product was obtained in the form of potassium salt which was dissolved in warm water and acidified by acetic acid to precipitate pure nucleobase. The crude product was recrystallized from acetic acid.

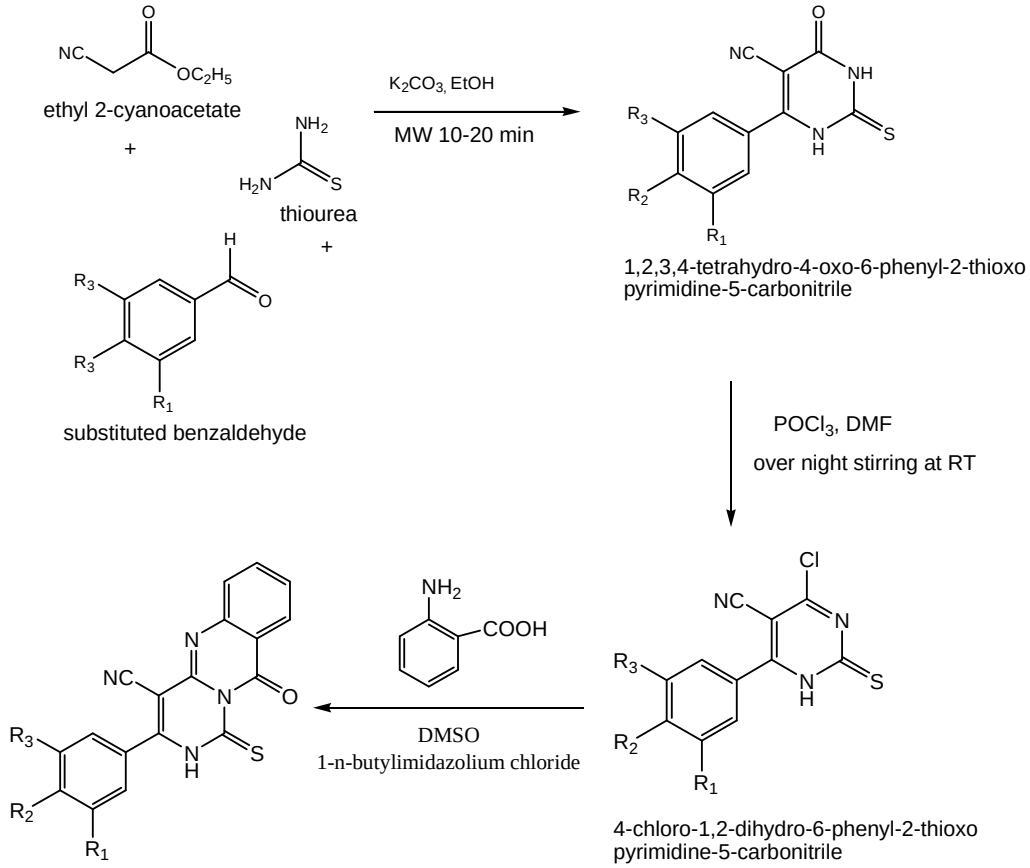
STEP 2: General procedure for synthesis of 4-chloro-1,2-dihydro-6-substituted phenyl-2-thioxopyrimidine-5-carbonitrile (TSIa-TSIVa) [18,20]

The compound **(TSI-TSIV)** (0.01mol) was dissolved in 10 ml DMF and stirred maintaining the temperature at 0-5^{O}C. To this cold stirring reaction mixture $POCl_3$ was added drop wise over

half an hour. The reaction mixture was stirred at 0-5^{O}C for 2 hr and then left for overnight stirring at RT. The completion of reaction was monitored by TLC. The workup was done by quenching into ice cold water followed by neutralization with sodium bicarbonate on which free flowing solid starts appearing. The crude product obtained was filtered, dried and recrystallized from *n*- Hexane.

STEP 3: General procedure for synthesis of 3-(substituted phenyl)-2,10-dihydro-10-oxo-1-thioxo-1*H*pyrimido[6,1-b]quinazoline-4-carbonitriles [21-24]

Equimolar mixture of **(TSIa-TSIVa)** and anthranillic acid in 0.5 g Ionic Liquid (1-*n*-butylimidazolium chloride) and 4.5 ml DMSO respectively was refluxed with stirring for 2-3 hrs. The reaction was monitored by TLC. The crystalline product obtained was filtered, dried and weighed to yield.



SCHEME 1

Spectral details (IR) are as given below (1H NMR of one representative series, TSI, TSIa and final compound T1 is given)

IR spectrum of TSI: 6-(4-fluorophenyl)-1,2,3,4-tetrahydro-4-oxo-2- thioxopyrimidine-5carbonitrile

IR (KBr): 3450 (N-H str.), 3121 (C-H Str., Ar-H), 1678 (C=O Str.), 2231 cm-1 (Nitrile Str.);1558 (C=C Aromatic str)1226(C=S str)1035 (C-F str); 1H NMR (DMSO): δ 7.397 (d, 2H, CH), 7.739-7.750 (d, 2H, CH), 13.128 (S, 1H, NH),13.37(S, 1H, NH)

IR spectrum of TSII: 6-(4-methoxyphenyl)-1,2,3,4-tetrahydro-4-oxo-2-thioxopyrimidine-5carbonitrile
IR (KBr): 3436 (N-H str.), 2946(C-H Str., Ar-H), 1678 (C=O Str.), 2229 cm-1 (Nitrile Str.);1552 (C=C Aromatic str)1134(C=S str),1271(O-CH3 Str.)

IR spectrum of TSII1: 6-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-4-oxo-2- thioxopyrimidine-5carbonitrile
IR (KBr): 3496 (N-H str.), 2940 (C-H Str., Ar-H), 1678 (C=O Str.), 2231 cm-1 (Nitrile Str.);1533 (C=C Aromatic str)1130(C=S str)1070 (C-Cl str), 1255(O-CH3 Str.)

IR spectrum of TSIV: 6-(3-chlorophenyl)-1,2,3,4-tetrahydro-4-oxo-2-thioxopyrimidine-5carbonitrile
IR (KBr): 3450 (N-H str.), 3121 (C-H Str., Ar-H), 1678 (C=O Str.), 2231 cm-1 (Nitrile Str.);1558 (C=C Aromatic str)1226(C=S str)1079 (C-Cl str)

IR spectrum of TSIa: 4-chloro-6-(4-fluorophenyl)-1,2-dihydro-2-thioxopyrimidine-5-carbonitrile
IR (KBr): 3076 (N-H str.), 3121 (C-H Str., Ar-H), 2227 cm-1 (Nitrile Str.);1602 (C=C Aromatic str)1240(C=S str)1079 (C-Cl Str) 1036 (C-F Str.); 1H NMR (DMSO): δ 7.4 (S, 1H, CH), 7.8 (S, 1H, CH), 3.2 (S, 1H, NH).

IR spectrum of TSIIa: 4-chloro-6-(4-methoxyphenyl)-1,2-dihydro-2-thioxopyrimidine-5-carbonitrile
IR (KBr): 3436 (N-H str.), 3112(C-H Str., Ar-H), 2229 cm-1 (Nitrile Str.);1670(C=C Aromatic str)1090(C=S str),1271(O-CH3 Str.)1027(C-Cl Str.)

IR spectrum of TSIIIa: 4-chloro-6-(3,4,5-trimethoxyphenyl)-1,2-dihydro-2-thioxopyrimidine-5-carbonitrile
IR (KBr): 3361 (N-H str.), 2940 (C-H Str., Ar-H), 2224 cm-1 (Nitrile Str.);1533 (C=C Aromatic str)1130(C=S str)1090 (C-Cl str), 1260(O-CH3 Str.)

IR spectrum of TSIVa: 4-chloro-6-(3-chlorophenyl)-1,2-dihydro-2-thioxopyrimidine-5-carbonitrile
IR (KBr): 3345 (N-H str.), 3073 (C-H Str., Ar-H), 2224 cm-1 (Nitrile Str.);1509 (C=C Aromatic str)1142(C=S str)1079(C-Cl Str), 1670(

IR spectrum of T1: 3-(4-fluorophenyl)-10-oxo-1-thioxo-2,10-dihydro-1H-pyrimido[6,1-b]quinazoline-4-carbonitrile
IR (KBr): 3363 (N-H str.), 2792 (C-H Str., Ar-H), 2364 cm-1 (Nitrile Str.);1509 (C=C Aromatic str)1142(C=S str), 1670(C=O Str),1103(C-F Str.); 1H NMR (DMSO): δ 6.96 (d, 2H, CH), 7.35 (d, 2H, CH), 2.00 (S, 1H, NH), 7.4-7.9 (m, 4H, Ar-H).

IR spectrum of T2: 3-(4-methoxyphenyl)-10-oxo-1-thioxo-2,10-dihydro-1H-pyrimido[6,1-b]quinazoline-4-carbonitrile
IR (KBr): 3364 (N-H str.), 2790 (C-H Str., Ar-H), 2364 cm-1 (Nitrile Str.);1500 (C=C Aromatic str)1142(C=S str), 1670(C=O Str), 1271(O-CH3 Str.)

IR spectrum of T3: 3-(3,4,5-trimethoxyphenyl)-10-oxo-1-thioxo-2,10-dihydro-1H-pyrimido[6,1-b]quinazoline-4-carbonitrile
IR (KBr): 3364 (N-H str.), 2790 (C-H Str., Ar-H), 2364 cm-1 (Nitrile Str.);1500 (C=C Aromatic str)1142(C=S str), 1670(C=O Str), 1271(O-CH3 Str.)

IR spectrum of T4: 3-(3-Chlorophenyl)-10-oxo-1-thioxo-2,10-dihydro-1H-pyrimido[6,1-b]quinazoline-4-carbonitrile
IR (KBr): 3364 (N-H str.), 2790 (C-H Str., Ar-H), 2364 cm-1 (Nitrile Str.);1500 (C=C Aromatic str)1142(C=S str), 1670(C=O Str), 1091 (C-Cl Str),

RESULTS AND DISCUSSION

Uracils (TSI-TSIV) were prepared by MWI methods and were treated with DMF/$POCl_3$ to give their chloro derivatives (TSIa-TSIVa).These chloro derivatives were then reacted with anthranilic acid in DMSO and catalytic amount of ionic liquid to give the title compounds.

The synthetic route for the preparation of title compounds is depicted in scheme 1. The assigned structure and molecular formula of the newly synthesized compounds were confirmed on the basis of their 1H NMR, and IR spectral analysis. The physical data of the compounds is given in **Table 1-Table 3**.

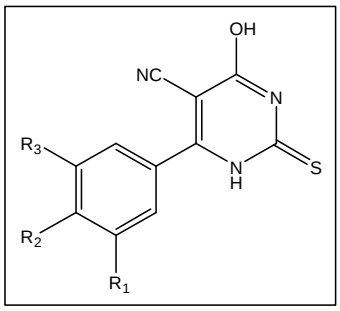


Table 1 Physical data of compounds TSI-TSIV

No.	R_1	R_2	R_3	Mp (^oC)	Yield (%)	M.F./M.W.
TSI	-H	-F	-H	270-272	87	$C_{11}H_6FN_3OS$/247.25
TSII	-H	$-OCH_3$	-H	252-254	78.54	$C_{12}H_9N_3O_2S$/259.28
TSIII	$-OCH_3$	$-OCH_3$	$-OCH_3$	310-314	85.33	$C_{14}H_{13}N_3O_4S$/319.34
TSIV	-Cl	-H	-H	166-168	82.64	$C_{11}H_6ClN_3OS$/263.7

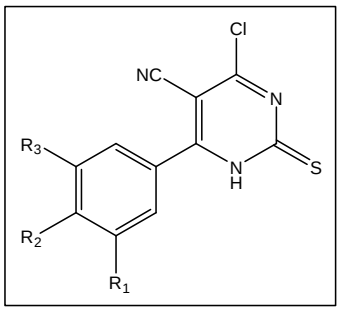


Table 2 Physical data of compounds TSIa-TSIVa

No.	R_1	R_2	R_3	Mp (^oC)	Yield (%)	M.F./M.W.
TSIa	-H	-F	-H	106-108	-90.22	$C_{11}H_5ClN_3FS$/265.69
TSIIa	-H	$-OCH_3$	-H	126-130	-86.42	$C_{12}H_8ClN_3OS$/277.73
TSIIIa	$-OCH_3$	$-OCH_3$	$-OCH_3$	226-228	-92.11	$C_{14}H_{12}ClN_3SO_3$/337.78
TSIVa	-Cl	-H	-H	100-102	94.11	$C_{11}H_7Cl_2N_3S$/282.15

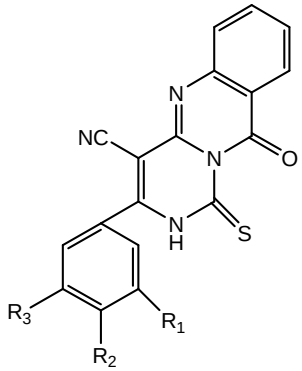


Table 3 Physical data of compounds T4

COMPOUND CODE	R1	R2	R3	Mp (^oC)	Yield (%)	M.F./MW	T LC*
T1	-H	-F	-H	93-95	65	$C_{18}H_9FN_4OS$/348.35	A
T2	-H	$-OCH_3$	-H	197-198	60	$C_{19}H_{12}N_4O_2S$/360.39	A
T3	$-OCH_3$	$-OCH_3$	$-OCH_3$	186-188	65	$C_{21}H_{16}N_4O_4S$/420.44	A
T4	-Cl	-H	-H	166-168	55	$C_{15}H_9ClN_4OS$/364.81	A

CONCLUSION

Thus we have successfully utilized the two green chemical techniques viz., use of Microwave and use of catalytic amount of ionic liquid in our synthetic scheme for preparation of the title compounds.

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