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One Step Iodine Promoted Synthesis of Imidazol-2-one and Pyrimidin-2-one

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ABSTRACT

Ecofriendly one step syntheses of symmetrical imidazol-2-ones and pyrimidin-2-ones/thiones have been reported by cyclisation of urea, thiourea, guanidine with aldehydes/ketones in presence of molecular iodine in ethanol by grinding in mortar by pestle. Symmetric bis-(2-aryl)-imidazol-2-ones and bis-(2-aryl)-pyrimidin-2-ones/thiones have been identified on the basis of IR, ^{1}H-NMR and mass spectral studies.

Keywords: Grindstone method, imidazol-2-one, pryimidin-2-one.

INTRODUCTION

Green chemistry offers clean synthesis, elimination of waste, mild reaction condition which save the environment.[1] The grinding is interesting as it is performed in absence of solvent leading to safe and energy efficient synthesis. The simple mechanochemical grinding by mortar and pestle is sufficient to get the desire product called hand grindstone method or mechanochemical method.[2,3] The molecular iodine is gaining importance as catalyst due to Lewis acid character, as its action as a condensing agent accelerates bond breaking and making in various organic transformations and cyclocondensations leading of bioactive heterocycles[4,5]. Due to Lewis acid nature of iodine, catalytic action of iodine is observed. The atmospheric oxygen also get involved in oxidative cyclisation known to be iodine promoted oxidation.[6]

The heterocycles such as imidazol-2-one and pyrimidin-2-one have no alternate in pharmaceutical sciences involving synthesis of new bioactive heterocycles based largely on the modification of structure.[7,8] Recently reported imidazole fused heterocycles have studied for their pharmacological action which expanded the scope in remedying various dispositions in clinical treatment includes hemeoxygenase inhibitors, antiaging, antiviral, anticancerand antimalarial properties.[9-11] On the other hand pyrimidin-2-ones have high pharmacological value and they are used as calcium channel blockers, neuropeptide Y antagonists (NPY).[12-14]

A thio-derivative of pyrimidin-2-ones acts as a cell-permeable molecule to block mitosis cell division and other derivatives also exhibit a wide spectrum of biological effects including antiviral and anticancer effects.[15] Recently many improved procedures for preparation of pyrimidones have been reported using phenyl pyruvic acid, Lewis acids, and heteropolyacids as catalyst; in addition to this methods ultrasound synthesis have also been reported.[16,17] Recently, Safari has been reported bis-aryl-pyrimidin-2-ones synthesis by Fe_3O_4-CNT nanocomposites by grinding using aldehydes, urea and ketone.[18]

Because of iodine is readily available, cheap, versatile, environment friendly and recyclable, this is an attempt to prove the utility of iodine in the single step synthesis of imidazol-2-ones and pyrimidin-2-ones by the reaction between urea/thiourea/guanidine with aldehydes and ketones employing hand grinding method.

MATERIALS AND METHODS

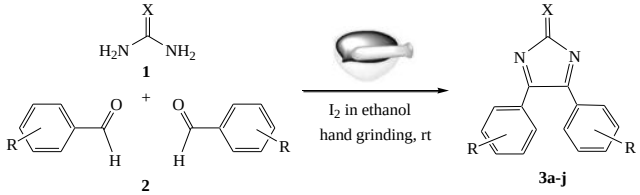
Melting points were determined on a digital melting point apparatus (Veego-DMP) and are uncorrected. Excess of iodine is removed by neutralisation with sodium thiosulphate after complete cyclisation. The spectral analysis of only representative **3a** and **5a** compounds was carried out and purity of the compounds checked till single spot visualised in TLC plate of silica gel using benzene: acetone (9:1) as solvent. The IR spectra were recorded on SHIMADZUFT-IR spectrophotometer using KBr pellets. ^{1}H-NMR spectra were recorded on a BRUKER AVANCE II 400 spectrophotometer with TMS as internal standard using DMSO-d^6 as solvents. Mass spectral measurements were carried out by EI method on a Q-TOF MACROMASS spectrometer at 70 eV.

2.2 Synthesis of bis-(2-aryl)-imidazol-2-ones (3a-j)

A mixture of urea (1 mmol) and aromatic aldehyde (2 mmol) was ground with molecular iodine for 5-10 min. in mortar by pestle of appropriate size. A solid mass obtained neutralised with aqueous solution of sodium thiosulphate to remove excess of iodine and left overnight. Then crude solid was washed with cold water, dried at room temperature. It was recrystalised in absolute ethanol in cold condition and identified as bis-(2-aryl)-imidazol-2-ones **(3a-j)**. This reaction was extended to synthesize compounds (**3b-j**) using urea, thiourea guanidine and various aromatic aldehydes (Scheme 1).

4,5-Diphenyl-imidazol-2-one (3a)

Brown solid, yield 84%, R*f* 0.66 (Benzene-Acetone, 9:1), m.p.187^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.38-7.17 (m, 6H, Aro-H), 7.52-8.14 (m, 4H, Aro-H). IR ν (cm^{-1}): 3059, 1678, 1449, 700. HRMS (ESI^+): *m/z* calculated for $C_{15}H_{10}N_2O$ [M+]: 233, 91. Anal. Calcd. For $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 75.56; H, 4.22; N, 12.03.



X = O, N, S etc R = -H, -CH_3, -Cl, -OH, -NO_2, -OCH_3

Exploration of iodine as a catalyst for the synthesis of (3a-j) Scheme 1

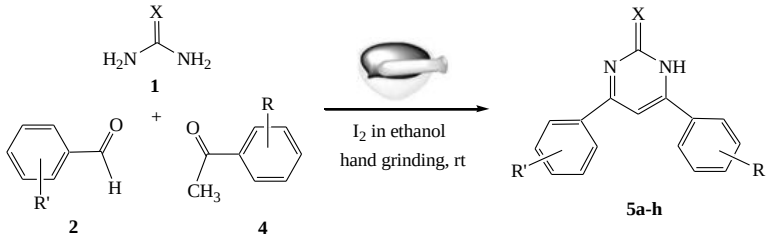
Catalyst	Time	Yield (%)									
Iodine	**(min)**	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**
0.5 ml	5-10	86	78	80	92	89	83	88	72	82	80
1.0 ml	5-10	74	66	71	80	76	71	70	63	77	79

2.3 Synthesis of bis-(2-aryl)-pyrimidin-2-ones/ thiones (5a-h)

A mixture of urea (1 mmol), aromatic aldehyde (1 mmol) and acetophenone (1mmol) was ground with molecular iodine for 5-10 min. in mortar by pestle of appropriate size and performing similar procedure afforded bis-(2-aryl)-pyrimidin-2-ones **(5a-h)**. This reaction was extended to synthesize compounds (**5b-h**) using urea, thiourea, various aromatic aldehydes and ketones (Scheme 2).

6-Phenyl-4-(p-methoxy-phenyl)-1H-pyrimidin-2-one (5a)

Brick red solid, yield 76%, R*f* 0.64 (Benzene-Acetone, 9:1), m.p. 210°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.6-7.80 (m, 5H, Aro-H), 6.8-7.17 (m, 4H, Aro-H), 3.37 (s, 1H, Pyri C-H), 2.50 (s, 3H, O-CH_3), 8.9 (s, 1H, N-H). IR ν (cm^{-1}): 3085, 1671, 1496, 767. HRMS (ESI^+): *m/z* calculated for $C_{17}H_{16}N_2O_2$ [M+]: 279, 278. Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 73.85; H, 5.29; N, 11. Found: C, 72.85; H, 5.71; N, 13.



X = O, S etc R and R' = -H, -OCH_3, -OH, -NO_2

Exploration of iodine as a catalyst for the synthesis of (5a-h) Scheme 2

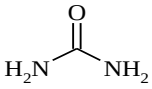
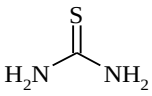
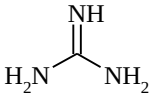
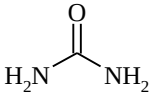
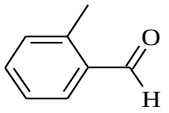
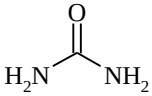
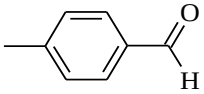
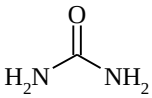
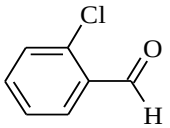
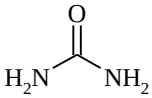
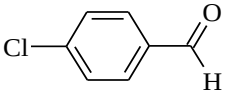
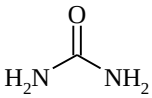
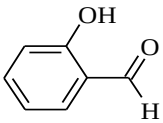
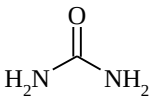
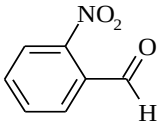
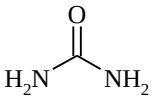
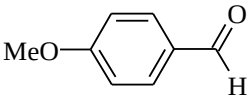
Catalyst	Time	Yield (%)							
Iodine	**(min)**	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**
0.5 ml	15-20	69	76	78	77	72	71	78	63
1.0 ml	15-20	66	71	74	72	71	65	79	64

RESULTS AND DISCUSSION

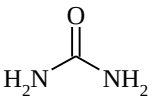
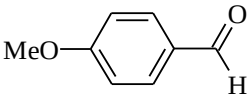
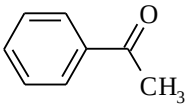
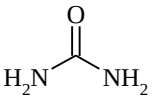
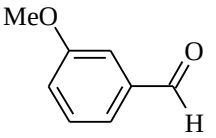
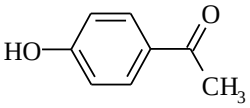
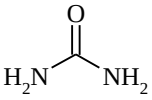
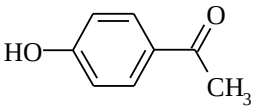
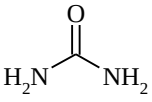
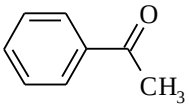
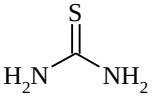
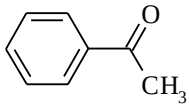
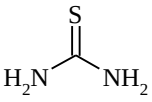
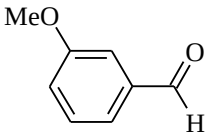
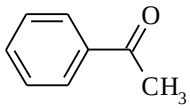
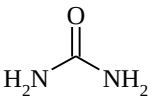
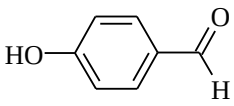
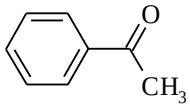
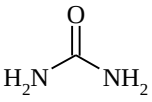
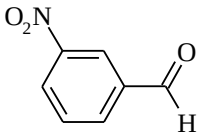
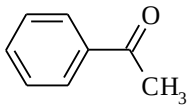
The oxidative cyclisation of urea/thiourea/guanidine with aldehydes/ketone in presence of iodine in ethanol to afford symmetric bis-(2-aryl)-imidazol-2-ones and bis-(2-aryl)-pyrimidin-2-ones/thiones is clean and proceeds even without heating energy. The dinucleophiles compounds such as urea, thiourea, guanidine undergo cyclisation with carbonyl compounds on continuous stirring in iodine in ethanol for about 5-15 min. All the synthesized compounds were adequately characterised by spectral data which are in good agreement with the structure of the title products. The IR spectrum[19] of the compounds (**3a**) and (**5a**) showed characteristic absorption band at 1678 and 1671 cm^{-1} indicated carbonyl group and ^{1}H-NMR

spectrum[20] indicated signal at δ 6.38-7.17 and 6.8-7.17ppm for the presence of aromatic ring respectively. In mass spectrum molecular ion peak was observed at *m/z* 233.43 and 279. Beside this elemental analysis was also found to be satisfactory. This environment friendly protocol is convenient in terms of high yield (63-92%) and products obtained in short duration of hand grinding (5-15 min).

Synthesis of bis-(2-aryl)-imidazol-2-ones, (3a-j), (Scheme-1)

Products	1	2	Yield (%)	mp (ºC)	time (min)
3a		Ph-CHO	86	187	5
3b		Ph-CHO	78	170	8
3c		Ph-CHO	80	114	10
3d			92	148	10
3e			89	156	7
3f			83	172	7
3g			88	185	7
3h			72	146	8
3i			82	205	7
3j			80	165	5

Synthesis of bis-(2-aryl)-pyrimidin-2-ones/ thiones, (5a-h), (Scheme-2)

Products	1	2	4	Yield (%)	mp (ºC)	time (min)
5a				69	210	15
5b				76	215	15
5c		Ph-CHO		78	180	15
5d		Ph-CHO		77	199	10
5e		Ph-CHO		72	265	20
5f				71	241	20
5g				78	150	10
5h				63	130	15

CONCLUSION

This communication have reported an one step iodine promoted synthesis of imidazol-2-ones and pyrimidin-2-ones/thiones by employing hand grinding method in single step. The use of molecular iodine as cheaper and recyclable material as well as clean and simple mechanochemical grinding is enough to get symmetrical bis-(2-aryl)-imidazol-2-ones (3a-j) and bis-(2-aryl)-pyrimidin-2-ones/thiones (5a-h) by the reaction between urea/thiourea/ guanidine with aldehydes and ketones.

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