REGULAR ARTICLE



One pot synthesis of pyrimidine-5-carbonitrile and pyrimidine-5-carboxamide using ammonium chloride under solvent free condition

J S AHER^{a,*}, A V KARDEL^b, M R GAWARE^c, D D LOKHANDE^c and A M BHAGARE^d ^aDepartment of Chemistry, K R T Arts, B H Commerce and A M Science College, Shivaji Nagar, Gangapur Road, Nashik, Maharashtra 422 002, India ^bDepartment of Chemistry, KGDM Arts, Commerce and Science College, Niphad, District Nashik, Maharashtra 422 303, India ^cDepartment of Chemistry, KPG Arts, Commerce and Science College Igatpuri, District Nashik, Maharashtra 422 402, India ^dDepartment of Chemistry, KKW Arts, Commerce and Science College, Pimaplgaon (B.), District Nashik, Maharashtra 422 209, India E-mail: js_aher@rediffmail.com; anantkardel11@gmail.com

MS received 18 December 2018; revised 9 March 2019; accepted 14 March 2019

Abstract. Pyrimidine-5-carbonitrile and pyrimidine-5-carboxamide were synthesized from the various substituted benzaldehyde, malononitrile and cyanoacetamide, urea/thiourea in the presence of ammonium chloride followed by characterization using IR, ¹H NMR spectroscopic technique.

Keywords. Ammonium chloride; Biginelli reaction; cyanoacetamide; malononitrile; substituted aromatic aldehyde; thiourea/urea.

1. Introduction

The increasing importance of pyrimidines and their derivatives as intermediates for the synthesis of biologically and industrially useful compounds prompted us to synthesize pyrimidine-5-carbonitrile derivatives. Pyrimidine and their derivatives are gaining the attention of the medicinal chemists in view of a long and notable history from the day of their discovery. The important pyrimidine compounds have a diverse application like bactericidal,¹ fungicidal,² analgesic,³ anti-inflammatory,⁴ antitumor agents,⁵ antioxidant,⁶ anti-HIV.⁷ They are also used as a calcium channel blocker. The pyrimidine and its fused derivatives have been widely used as drugs to treat various diseases. Pyrimidines occur in some pesticides and plant growth regulators.

Dipen K Sureja et al.,⁸ documented the synthesis of pyrimidine -5-carbonitrile in three different methods such as the presence of conc. hydrochloric acid and ethanol, conc. sulphuric acid and ethanol in the microwave assisted method, CH₃COONa and water by green chemistry method approach. Navan H. Bhuva⁹ and co-worker documented the synthesis of pyrimidine-5-carboxamide as an intermediate step obtained by three-component aromatic aldehyde, thiourea, and malononitrile in the presence of methanol and hydrochloric acid resulting in pyrimidine-5-carbonitrile, which on reaction with conc. sulphuric acid gives pyrimidine-5carboxamide. Dipti R Patil¹⁰ and co-workers in 2010 also documented the same synthesis in the presence of phosphorus pentaoxide and ethanol. However, all the reported methods suffered several drawbacks such as long reaction time, harsh reaction conditions, anhydrous conditions, stoichiometric amounts, hazardous radiation, use of costly apparatus, and gave unsatisfactory results. Therefore, in our present work, we have used the least expensive and easily available catalyst as well as a mild and neutral reaction condition for the synthesis

^{*}For correspondence

J. S. Aher: Affiliated to Savitribai Phule Pune University (Formerly University of Pune), Maharashtra, India.

Electronic supplementary material: The online version of this article (https://doi.org/10.1007/s12039-019-1633-6) contains supplementary material, which is available to authorized users.



 $\mathbf{R} = C_6H_5$, 2-(Cl)-C₆H₄, 4-(Cl)-C₆H₄, 4-(NO₂)-C₆H₄, 4-(CH₃)-C₆H₄. $\mathbf{X} = \mathbf{O}$, S

Scheme 1. Synthesis of Pyrimidine-5-Carbonitrile and Pyrimidine-5-Carboxamide.

of pyrimidine-5- carbonitrile. We have developed a new method for synthesis of pyrimidine-5-carboxamide the use of cyanoacetamide.

Various methods have been reported *vis-à-vis* the synthesis of pyrimidine derivatives.¹¹ Few one-pot syntheses have been published using aromatic aldehyde cyano ethyl acetate and thiourea.^{12–14} Hence, we wish to report the results obtained from the study of the preparation of pyrimidine-5-carbonitrile and pyrimidine-5-carboxamide and its derivatives with ammonium chloride (NH₄Cl) as easily available catalyst under neutral and solvent-free conditions (Scheme 1). The procedure gives the product in good yields and avoids the problems like cost and handling safety associated with the use of the solvent. The method decreases reaction time because of the increase in the reactivity of the reactant in the solid state at the reaction temperature of $110 \,^\circ$ C.

2. Experimental

The reagents used are of research grade and are purchased from SD Fine-Chem and Merck laboratories. The melting points have been recorded in an open capillary method and are uncorrected. The melting points are compared with the literature report. The products are characterized by using Fourier Transform Infrared spectra (FT-IR) and ¹H Nuclear Magnetic Resonance (¹H NMR). The FT-IR spectra are recorded on Shimadzu FT-IR spectrometer while ¹H NMR spectra have been recorded on Bruker (500 MHz) using DMSO-d6 as a solvent.

2.1 General procedure for the synthesis of pyrimidine-5-carbonitrile and pyrimidine-5-carboxamide

In a 100 mL round bottom flask a mixture of benzaldehyde (0.24 g 2 mmol/L), malononitrile (0.12 g 2 mmol/L), urea

(0.18 g 3 mmol/L) and NH₄Cl (0.36 g 0.8 mmol/L) were heated in the oil bath under stirring at 110 °C for 4 h. The progress of the reaction was monitored using TLC. After completion of the reaction, the reaction mixture was cooled at room temperature and poured in crushed ice to obtain the solid product. The crude product was filtered and washed with cold water and recrystallized from ethyl acetate: n-hexane at a 1:3 ratio to obtain an analytical sample for spectral analysis.

2.2 Spectral data of synthesized compounds

2.2*a* Entry-4*a*: 4-Amino-2-hydroxy-6-phenylpyrimidine-5 -carbonitrile: Yield: 82%; C₁₁H₈N₄O: M.p. 179–181 °C (Lit M.p. 179 °C) IR (cm⁻¹): v_{O-H} 3415, v_{N-H} 3373, v_{Ar-H} 3082, 3032, $v_{C\equiv N}$ 2220, $v_{C=N}$ 1589, $v_{ArC=C}$ 1556, v_{C-N} 1340; ¹H NMR (δ , ppm in dmso-d6, 500 MHz): δ 8.55 (s, 2H,-NH₂), δ 7.96 (s, 1H, -OH), δ 7.71–7.61 (m, 5H, Ar-H).

2.2b Entry-4b 4-Amino-6-(2-chlorophenyl)-2-hydroxypyrimidine-5-carbonitrile: Yield: 75%; C₁₁H₇N₄OCl: M.p. 162–164 °C (Lit M.p. 164 °C) IR (cm⁻¹): v_{O-H} 3415, v_{Ar-H} 3091, 3049, $v_{C=N}$ 2225, $v_{C=N}$ 1579, v_{C-N} 1286, v_{Ar-Cl} 1128; ¹HNMR (δ , ppm in dmso-d6, 500 MHz): δ 8.68 (s, 2H, -NH₂), δ 8.02 (s, 1H, –OH) δ 7.71–7.57 (m, 4H, Ar-H).

2.2*c* Entry-4*d* 4-Amino-6-(4-nitrophenyl)-2-hydroxypyrimidine-5-carbonitrile: Yield: 74%; C₁₁H₇N₅O₃: M.p. 221–223 °C (Lit M.p. 224 °C) IR (cm⁻¹): v_{O-H} 3369, v_{Ar-H} 3034, 2920, $v_{C=N}$ 2218, $v_{C=N}$ 1589, $v_{ArC=C}$ 1566, v_{N-O} 1440, v_{C-N} 1317; ¹H NMR (δ , ppm in dmso-d6, 500 MHz): δ 8.40 (s, 2H, - NH₂), δ 7.99 (s, 1H, –OH), δ 7.97–7.18 (m, 4H, Ar-H).

2.2*d* Entry-4 *h* 4-Amino-6-(4-chlorophenyl)-2-mercaptopyrimidine-5-cabonitrile: Yield: 81%; C₁₁H₇N₄OCl M.p. 123–125 °C (Lit M.p. 125 °C) IR (cm⁻¹): v_{Ar-H} 3032, 2953, $v_{C\equiv N}$ 2218, $v_{ArC=C}$ 1602, 1566, v_{C-N} 1317, v_{Ar-Cl} 1180, v_{S-H} 2610; ¹H NMR (δ , ppm in dmso-d6, 500 MHz): δ 8.56 (s, 2H, - NH₂), δ 7.96 (s, 1H, –OH), δ 7.94–7.71 (m, 4H, Ar-H).

Table 1. Synthesis of pyrimidine-5-carbonitrile andpyrimidine-5-carboxamide using ammonium chloride undersolvent-free condition.

Compound	Ar	Х	Yield %	M.p. (°C)
4a	C_6H_5	0	82	179–181 °C
4b	2-(Cl)-C ₆ H ₄	0	75	180-182 °C
4c	$4-(Cl)-C_6H_4$	0	84	162-164°C
4d	$4-(NO_2)-C_6H_4$	0	74	221-223 °C
4e	4-(CH ₃)-C ₆ H ₄	0	72	148-150°C
4f	C_6H_5	S	90	152-154°C
4g	2-(Cl)-C ₆ H ₄	S	85	148-150°C
4h	$4-(Cl)-C_6H_4$	S	81	123-125 °C
4i	$4-(NO_2)-C_6H_4$	S	82	190-192°C
4j	4-(CH ₃)-C ₆ H ₄	S	84	150-152 °C
6a	C_6H_5	0	79	120-122 °C
6b	2-(Cl)-C ₆ H ₄	0	86	176-178°C
6c	$4-(Cl)-C_6H_4$	0	89	218-220°C
6d	$4-(NO_2)-C_6H_4$	0	86	209-210°C
6e	$4-(CH_3)-C_6H_4$	0	84	191-193°C
6f	C_6H_5	S	75	118-120°C
6g	2-(Cl)-C ₆ H ₄	S	78	161-163 °C
6h	$4-(Cl)-C_6H_4$	S	84	222-224°C
6i	$4-(NO_2)-C_6H_4$	S	81	210-212 °C
6j	$4-(CH_3)-C_6H_4$	S	80	150–152 °C

2.2e Entry-6a 4-Amino-2-hydroxy-6-phenylpyrimidine-5 -carboxamide: Yield: 79%; C₁₁H₁₀N₄O₂ M.p. 120–122 °C IR (cm⁻¹): v_{O-H} 3396, v_{N-H} 3350, v_{Ar-H} 3157, $v_{ArC=C}$ 1689, 1595, $v_{C=N}$ 1492, v_{C-N} 1371; ¹H NMR (δ , ppm in dmso-d6, 500 MHz) δ 7.95 (s, 2H, - NH₂), δ 8.19 (s, 1H, – OH), δ 7.93 (s, 2H, H₂N-C=O), δ 7.76–7.75 (m, 5H, Ar-H).

3. Results and Discussion

The presence of electron donating and electron withdrawing group in the aromatic ring has played a crucial role in determining the yield of the product. From Table 1 it is observed that due to the presence of electron donating group exhibiting (+I) effect in pyrimidine-5-carbonitrile, the yield of the product has decreased, while the presence of electron withdrawing group possessing (-I) effect has enhanced the yield of the product. This explains the nucleophilic attack or more positively carbonyl carbon. Similar trends have also been seen in the case of carboxamide. We have reported a unique, simple and solvent-free contemporary synthesis strategy for pyrimidine-5-carbonitrile and pyrimidine-5-carboxamide. Besides the correct values of IR, the ¹H NMR of compounds are in good agreement with the assigned structure. In addition, the latter compound was used as a good source to enrich the synthesis of heterocyclic chemistry with several new pyrimidine-5-carbonitrile and pyrimidine-5-carboxamide its derivatives.

4. Conclusions

In conclusion, we have developed a simple, quick and eco-friendly method for synthesis of pyrimidine-5carbonitrile and pyrimidine-5-carboxamide with short reaction time. It is also inexpensive with the easily available catalyst under the neutral and solvent-free conditions.

Supplementary Information (SI)

Supplementary information is available at www.ias.ac.in/ chemsci.

Acknowledgements

The authors are thankful to Maratha Vidya Prasarak Samaj, Nashik for providing infrastructure for research and spectral data. The authors also express their sincere thanks to the Principal, K.R.T. Arts B. H. Commerce and A.M. Science (KTHM) College, Gangapur Road, Nashik and the Principal, K. G. D. M. Arts, Commerce and Science College, Niphad.

References

- 1. Brown R C D 1998 recent developments in solid phase organic synthesis J. Chem. Soc. Perkin Trans. 1 3293
- Pershin N G, Sherbakova L I, Zykova T N and Sakolova V N 1972 Antibacterial activity of pyrimidine and pyrrolo-(3,2-d)-pyrimidine derivatives *Pharmacol. Taksiko* 35 466
- 3. Metolcsy G 1971 Structure-activity correlations and mode of action of some selected types of antifungal compounds *World Rev. Pest Contr.* **10** 50
- Regnier G L, Canevar R J, Canevar J C, Douarec L, Halstop S and Daussy J 1972 Triphenyl propyl piper zine derivatives as new potent analgesic substances *J. Med. Chem.* 15 295
- Winter C A, Fisley E A and Nuss G W 1962 Carrageenininduced edema in hind paw of the rat as an assay for anti-inflammatory drugs *Proc. Soc. Experiment. Biol. Med.* 111 544
- Padmaja A T, Payani G D, Reddy V and Padmavathi 2009 Synthesis, antimicrobial and antioxidant activities of substituted pyrazoles, isoxazoles, pyrimidine and thioxopyrimidine derivatives *Eur. J. Med. Chem.* 44 4557
- Selvam T P, James C R, Dniandev P V and Valzita S K 2012 A mini review of pyrimidine and fused pyrimidine marketed drugs *Res. Pharm.* 2 01
- Dipen K S, Sandip P D and Kantilal R V 2016 Aqua mediated sodium acetate catalysed one-pot synthesis of pyrimidine derivatives as anti-inflammatory and antioxidant agent *Der Pharma Chem.* 8 105
- 9. Nayan H B, Vrajlal K G, Pankaj M S, Pratik K T, Viral J F and Viresh H S 2014 Synthesis of

J. Chem. Sci. (2019) 131:54

novel 2-mercapto-4-(p-aminophenyl sulphonylamino)-6-(aryl)-pyrimidine-5-carboxamide derivatives via the Biginelli reaction *Int. Lett. Chem. Phys. Astronom.* **17** 168

- Dipti R P, Sanali M S, Madhukar B D and Prashant V A 2010 One step synthesis of 6-amino-5-cyano-4phenyl-2-mercapto pyrimidine using phosphorus pentoxide Open Catal. J. 3 83
- 11. Mojtahedi M M, Saidi M R, Shirzi J S and Bolourtchian M 2002 Microwave promoted efficient synthesis of substituted uracils and thiouracils under solvent-free conditions *Synth. Commun.* **32** 851
- Ma Y, Qian C, Wang L and Yang M 2000 Lanthanide Triflate catalysed biginelli reaction. One-pot synthesis of dihydropyrimidinones under solvent free conditions *Org. Chem.* 65 3864
- 13. Li J-T, Lin Z-P, Han J-F and Li T-S 2004 One-pot synthesis of 4-oxo-2-thioxohexahydropyrimidines catalyzed by potassium carbonate under ultrasound *Synth*. *Synth. Commun.* **34** 2623
- 14. Kambe S and Salto K H 1979 A one-pot synthesis of 4oxo-2-thioxopyrimidine derivatives by the ternary condensation of ethyl cyanoacetate, aldehydes, and thiourea *Synthesis* **4** 287