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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]
[a]Department of Chemistry, K R T Arts, B H Commerce and A M Science College, Shivaji Nagar, Gangapur Road, Nashik, Maharashtra 422 002, India
[b]Department of Chemistry, KGDM Arts, Commerce and Science College, Niphad, District Nashik, Maharashtra 422 303, India
[c]Department of Chemistry, KPG Arts, Commerce and Science College Igatpuri, District Nashik, Maharashtra 422 402, India
[d]Department 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

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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, ^{1}H 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, CH_3COONa and water by green chemistry method approach. Nayan H. Bhuva[9] 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-5-carboxamide. Dipti R Patil[10] 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.

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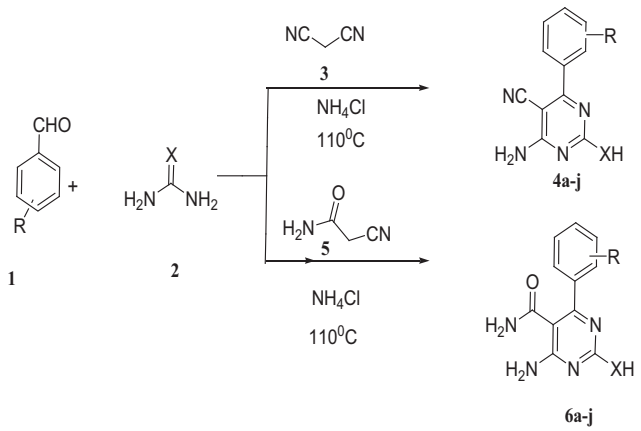

R= C_6H_5, 2-(Cl)-C_6H_4, 4-(Cl)-C_6H_4, 4-(NO_2)-C_6H_4, 4-(CH_3)-C_6H_4. **X**= O, S

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 (NH_4Cl) 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 °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 ^{1}H Nuclear Magnetic Resonance (^{1}H NMR). The FT-IR spectra are recorded on Shimadzu FT-IR spectrometer while ^{1}H 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 NH_4Cl (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*

2.2a Entry-4a: 4-Amino-2-hydroxy-6-phenylpyrimidine-5 -carbonitrile: Yield: 82%; $C_{11}H_8N_4O$: M.p. 179−181 °C (Lit M.p. 179 °C) IR (cm^{-1}): ν_{O-H} 3415, ν_{N-H} 3373, ν_{Ar-H} 3082, 3032, $\nu_{C\equiv N}$ 2220, $\nu_{C=N}$ 1589, $\nu_{ArC=C}$ 1556, ν_{C-N} 1340; ^{1}H NMR (δ, ppm in dmso-d6, 500 MHz): δ 8.55 (s, 2H,–NH_2), 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-hydroxy-pyrimidine-5-carbonitrile: Yield: 75%; $C_{11}H_7N_4OCl$: M.p. 162−164 °C (Lit M.p. 164 °C) IR (cm^{-1}): ν_{O-H} 3415, ν_{Ar-H} 3091, 3049, $\nu_{C\equiv N}$ 2225, $\nu_{C=N}$ 1579, ν_{C-N} 1286, ν_{Ar-Cl} 1128; ^{1}HNMR (δ, ppm in dmso-d6, 500 MHz): δ 8.68 (s, 2H, -NH_2), δ 8.02 (s, 1H, –OH) δ 7.71–7.57 (m, 4H, Ar-H).

2.2c Entry-4d 4-Amino-6-(4-nitrophenyl)-2-hydroxy-pyrimidine-5-carbonitrile: Yield: 74%; $C_{11}H_7N_5O_3$: M.p. 221−223 °C (Lit M.p. 224 °C) IR (cm^{-1}): ν_{O-H} 3369, ν_{Ar-H} 3034, 2920, $\nu_{C\equiv N}$ 2218, $\nu_{C=N}$ 1589, $\nu_{ArC=C}$ 1566, ν_{N-O} 1440, ν_{C-N} 1317; ^{1}H NMR (δ, ppm in dmso-d6, 500 MHz): δ 8.40 (s, 2H, - NH_2), δ 7.99 (s, 1H, –OH), δ 7.97–7.18 (m, 4H, Ar-H).

2.2d Entry-4 h 4-Amino-6-(4-chlorophenyl)-2-mercapto-pyrimidine-5-cabonitrile: Yield: 81%; $C_{11}H_7N_4OCl$ M.p. 123−125 °C (Lit M.p. 125 °C) IR (cm^{-1}): ν_{Ar-H} 3032, 2953, $\nu_{C\equiv N}$ 2218, $\nu_{ArC=C}$ 1602, 1566, ν_{C-N} 1317, ν_{Ar-Cl} 1180, ν_{S-H} 2610; ^{1}H NMR (δ, ppm in dmso-d6, 500 MHz): δ 8.56 (s, 2H, - NH_2), δ 7.96 (s, 1H, –OH), δ 7.94–7.71 (m, 4H, Ar-H).

Table 1. Synthesis of pyrimidine-5-carbonitrile and pyrimidine-5-carboxamide using ammonium chloride under solvent-free condition.

Compound	Ar	X	Yield %	M.p. (°C)
4a	C_6H_5	O	82	179−181 °C
4b	2-(Cl)-C_6H_4	O	75	180−182 °C
4c	4-(Cl)-C_6H_4	O	84	162−164 °C
4d	4-(NO_2)-C_6H_4	O	74	221−223 °C
4e	4-(CH_3)-C_6H_4	O	72	148−150 °C
4f	C_6H_5	S	90	152−154 °C
4g	2-(Cl)-C_6H_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_6H_4	S	84	150−152 °C
6a	C_6H_5	O	79	120−122 °C
6b	2-(Cl)-C_6H_4	O	86	176−178 °C
6c	4-(Cl)-C_6H_4	O	89	218−220 °C
6d	4-(NO_2)-C_6H_4	O	86	209−210 °C
6e	4-(CH_3)-C_6H_4	O	84	191−193 °C
6f	C_6H_5	S	75	118−120 °C
6g	2-(Cl)-C_6H_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%; $C_{11}H_{10}N_4O_2$ M.p. 120−122 °C IR (cm^{-1}): ν_{O-H} 3396, ν_{N-H} 3350, ν_{Ar-H} 3157, $\nu_{ArC=C}$ 1689, 1595, $\nu_{C=N}$ 1492, ν_{C-N} 1371; ^{1}H NMR (δ, ppm in dmso-d6, 500 MHz) δ 7.95 (s, 2H, - NH_2), δ 8.19 (s, 1H, –OH), δ 7.93 (s, 2H, H_2N-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 ^{1}H 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-5-carbonitrile 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.

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