

SYNTHESIS AND CHARACTERIZATION OF SOME NEW BIOLOGICALLY ACTIVE PYRIMIDINE DERIVATIVES

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ABSTRACT

Pyrimidine Compounds have occupied an important position in natural and synthetic organic chemistry, mainly due to their wide range of biological activities. Here we have synthesized some new pyrimidine compounds using urea, ethyl cyanoacetate and different aldehydes, in moderate to good yields.

Keywords: Pyrimidine, multi-component reactions, biological activity.

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INTRODUCTION

The heterocyclic aromatic systems are of much greater importance than the constituent monocyclic compounds. The appearance of qualitatively new properties of an annulated molecule, enlargement of the possibility of varying pharmacophore groups in different positions of the molecule and ability of the latter to interact with a wider spectrum of receptors adopting various conformations are apparently of crucial importance.

The aspect of uracil and its derivatives was well recognized by organic as well as biologists. With the development of clinically useful anticancer and antiviral drugs, there has recently been remarkable interest in the synthetic manipulation of uracils. Multi-Component reactions, in which multiple reactions are combined into one synthetic operation, have been used extensively to form carbon-carbon bonds in synthetic chemistry. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in single procedural steps, avoid the complicated purification operation and allow savings of both solvents and reagents. In the past decade, there has been a tremendous development in three and four component reactions and great efforts continue to be made to develop new multicomponent reactions. The need to reduce the amount of toxic waste and by-product arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods.

In modern years, pyrimidine and dihydropyrimidines have been in an important position in natural and synthetic organic chemistry, due to their wide range of biological activities, such as antibacterial, antiviral, antihypertensive and antitumor effects and their effects as calcium channel blockers.¹⁻¹³ The development of efficient and environmentally acceptable synthetic methods is an important task of modern chemistry. Conventional organic syntheses are generally based on homogeneous catalysts. However, homogeneous reactions suffer disadvantages in separation, isolation of products and so on. From the view point of green chemistry, the use of heterogeneous catalysts is desirable. The consequential advantages of heterogeneous catalysts from the environmental and economic points of view are clearly understandable, because these procedures are low costing and the production of the waste material is decreased. In contrast to the extensive studies involving heterogeneous acid catalysts, fewer efforts have been made to develop heterogeneous base catalysts. Several solid bases have been reported as being effective in this respect, such as zeolites,¹⁴ alkali metals supported on alumina,¹⁵ clay minerals, metal oxides such as magnesium oxide,¹⁶ and mixed metal oxides, for example, magnesium – lanthanum mixed oxide.

Among these solid bases, MgO recently has been studied using a novel but simple procedure, was systematically investigated as a heterogeneous base catalyst for reactions taking place in the liquid phase, specifically the Michael addition and the Knoevenagel condensation.

EXPERIMENTAL

The chemicals and solvents used for the experimental work were commercially procured from Sd. fine Chemicals. The melting points of all synthesized compounds were determined by open tube capillary in the Celsius scale and uncorrected. IR spectra were recorded using KBr pellets on Perkin Elmer spectrophotometer, ¹H-NMR spectra of the final compounds were recorded on Bruker NMR spectrometer (300 MHz).

General Procedure for Synthesis of Compounds 1(a-i)

A mixture of ethyl cyanoacetate (10 mmol), thiourea (10 mmol) and appropriate aldehydes (10 mmol) was stirred in a solution of sodium acetate for 48 to 54 hr and then the reaction mixture was poured in crushed ice. Then it was acidified and the product obtained was filtered off, then dried and recrystallized from suitable solvents.

General Procedure for Synthesis of Compounds 2 (a-i)

The product obtained in step 1, compound 1 (10 mmol), phosphorous pentachloride (10 mmol) and phosphorous oxychloride (20 ml) was heated in a water bath for 4 to 4.5 hours and the reaction mixture was poured in crushed ice. The product obtained was filtered off, then dried and recrystallized from a suitable solvent.

General Procedure for Synthesis of Compounds 3 (a-d)

A mixture of compound 2 (5 mmol) and hydrazine hydrate (5 mmol) was taken in 20 ml methanol and stirred for nine hours. The product obtained was filtered, dried and recrystallized from a suitable solvent.

General Procedure for Synthesis of Compounds 4 (a-b)

A mixture of compound 3 (5 mmol), and an aldehyde (5 mmol) was taken in 20 ml methanol and refluxed for four hours. After that, the reaction mixture was poured in crushed ice. The product obtained was filtered, dried and recrystallized from a suitable solvent.

Spectral Data of Selected Compounds

Compound 1a: Yield 68%, m. p. 271-272°C; IR (KBr) (ν cm^{-1}); 1712 (C=O), 2230 (CN), 3301 (NH), 1370- 1024 (C-N Bending), 1458, 1590 (C=C, Ar), 1610 (C=C) ; ¹H NMR (300 MHz) (δ , ppm); 7.01-7.28 (m, 5H, Ar-H), 7.46 (s, 1H, Sec NH), 12.13 (s, 1H, amine).

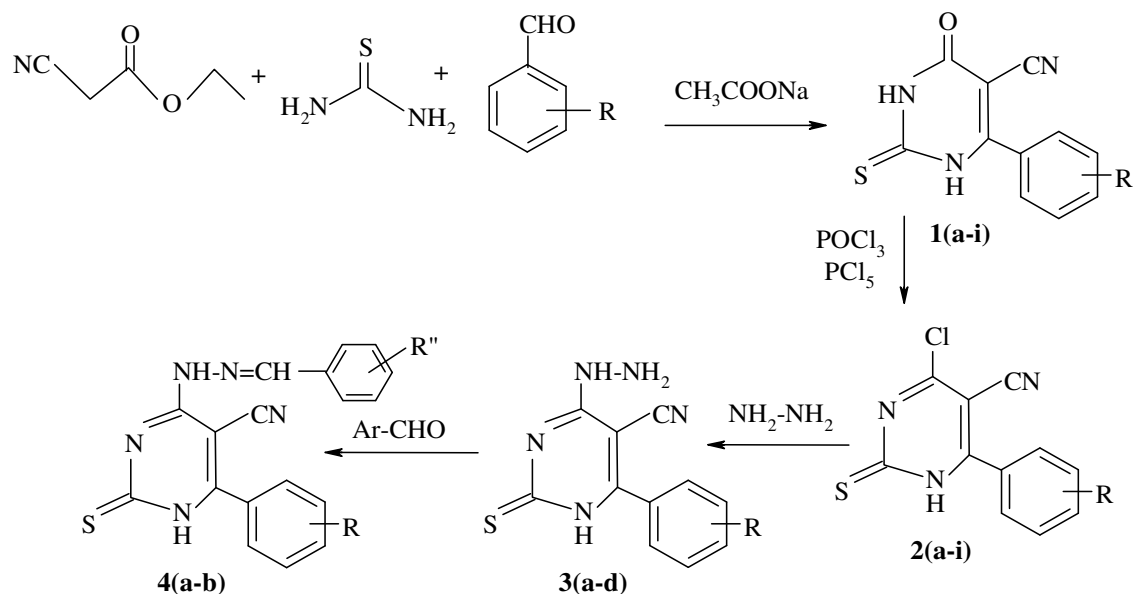
Compound 1b: Yield 84%, m. p. 55-57°C; IR(KBr) (ν cm^{-1}); 1716 (C=O), 2233 (CN), 3305 (NH), 1371- 1021 (C-N Bending), 1462, 1600 (C=C, Ar), 1602 (C=C) ; ¹H NMR (300 MHz) (δ , ppm); 3.78 (3H, s, OCH₃), 7.05-7.31 (m, 4H, Ar-H), 7.51 (s, 1H, Sec NH), 12.09 (s, 1H, amine).

Compound 1c: Yield 72%, m. p. 60-62°C; IR(KBr) (ν cm^{-1}); 1693 (C=O), 2240 (CN), 3286 (NH), 1261 (C-N Bending), 1438 (C=C), 3181 (C-H), 3500 (OH); ¹H NMR (300 MHz) (δ , ppm); 7.05-7.31 (m, 4H, Ar-H), 7.51 (s, 1H, Sec NH), 10.12 (1H, s, OH), 12.09 (s, 1H, amine).

Compound 1d: Yield 85%, m. p. 74-76°C; IR (KBr) (ν cm^{-1}); 840 (C-Cl), 1682 (C=O), 2232 (CN), 3268 (NH), 1246 (C-N Bending), 1445 (C=C), 3176 (C-H).

Compound 1e: Yield 72%, m. p. 68-70 °C; ¹H NMR (300 MHz) (δ , ppm); 7.16-7.37 (m, 4H, Ar H), 7.55 (s, 1H, Sec NH), 12.19 (s, 1H, NH amine).

Compound 1f: Yield 90%, m. p. 64-66°C; ¹H NMR (300 MHz) (δ , ppm); 7.21-7.46 (m, 4H, Ar H), 7.55 (s, 1H, Sec NH), 12.24 (s, 1H, NH amine).



1a, R = H
 1b, R = *p*-OMe
 1c, R = 3-OH
 1d, R = 3-Cl
 1e, R = 4-Cl
 1f, R = 4-NO₂
 1g, R = 2-Cl
 1h, R = 3-NO₂
 1i, R = 4-OH

2a, R = H
 2b, R = *p*-OMe
 2c, R = 3-OH
 2d, R = 3-Cl
 2e, R = 4-Cl
 2f, R = 4-NO₂
 2g, R = 2-Cl
 2h, R = 3-NO₂
 2i, R = 4-OH

Scheme-1

3a, R = 3-Cl
 3b, R = 4-NO₂
 3c, R = 2-OH
 3d, R = 4-OH

4a, R = 4-NO₂, R'' = 4-Cl
 4b, R = 4-NO₂, R'' = 3-OH

Compound 1g: Yield 80%, m. p. 55-57 °C; IR (KBr) (ν cm⁻¹); 848 (C-Cl), 1673 (C=O), 2253 (CN), 3257 (NH), 1242 (C-N Bending), 1438 (C=C), 3168 (C-H).

Compound 1h: Yield 78%, m. p. 130-132 °C; ¹H NMR (300 MHz) (δ , ppm); 7.24-7.51 (m, 4H, Ar H), 7.46 (s, 1H, Sec NH), 12.16 (s, 1H, NH amine).

Compound 1i: Yield 80%, m. p. 168-170 °C; IR(KBr) (ν cm⁻¹); 1688(C=O), 2234 (CN), 3277 (NH), 1252 (C-N Bending), 3176 (C-H), 1431 (C=C), 3512(OH);¹H NMR (300 MHz) (δ , ppm); 7.12-7.33 (m, 4H, Ar H), 7.48 (s, 1H, Sec NH), 10.10 (1H, s, OH) 12.11 (s, 1H, amine).

Table-1: Physical and Analytical Data of the Prepared Compounds (1a-i), (2a-i), (3a-d) and (4a-b)

S. No.	Compound Code	Molecular Formula	Molecular Wt.	Melting Point (°C)	Yield %
1	1a	C ₁₁ H ₇ N ₃ SO	229.0	271-272	68
2	1b	C ₁₂ H ₉ N ₃ O ₂ S	259.0	55-57	84
3	1c	C ₁₁ H ₇ N ₃ O ₂ S	245.0	60-62	72
4	1d	C ₁₁ H ₆ N ₃ SOCl	263.5	74-76	85
5	1e	C ₁₁ H ₆ N ₃ SOCl	263.5	68-70	72
6	1f	C ₁₁ H ₆ N ₄ O ₃ S	274.0	64-66	90
7	1g	C ₁₁ H ₆ N ₃ SOCl	263.5	55-57	80
8	1h	C ₁₁ H ₆ N ₄ O ₃ S	274.0	130-132	78
9	1i	C ₁₁ H ₇ N ₃ O ₂ S	245.0	168-170	80
10	2a	C ₁₁ H ₆ N ₃ SCl	246.5	186-188	73
11	2b	C ₁₂ H ₈ N ₃ SOCl	277.5	178-180	88

12	2c	C ₁₁ H ₆ N ₃ SOCl	263.5	212-214	70
13	2d	C ₁₁ H ₅ N ₃ SCl ₂	282.0	160-162	81
14	2e	C ₁₁ H ₅ N ₃ SCl ₂	282.0	160-162	76
15	2f	C ₁₁ H ₅ N ₄ O ₂ SCl	292.5	208-210	80
16	2g	C ₁₁ H ₅ N ₃ SCl ₂	282.0	158-160	84
17	2h	C ₁₁ H ₅ N ₄ O ₂ SCl	292.5	158-160	77
18	2i	C ₁₁ H ₆ N ₃ SOCl	263.5	218-220	73
19	3a	C ₁₁ H ₈ N ₅ SCl	277.5	212-214	65
20	3b	C ₁₁ H ₈ N ₆ SO ₂ Cl	288.0	181-183	68
21	3c	C ₁₁ H ₉ N ₅ SOCl	259.0	191-193	60
22	3d	C ₁₁ H ₉ N ₅ SOCl	259.0	224-226	62
23	4a	C ₁₈ H ₁₁ N ₆ O ₂ SCl	410.5	188-190	66
24	4b	C ₁₈ H ₁₂ N ₆ O ₃ S	392.0	157-159	61

Compound 2a: Yield 73%, m. p.186-188 °C; IR (KBr) (ν cm⁻¹); 1476, 1618 (C=C, Ar) 1617 (C=C), 1678 (C=N), 2230 (CN), and 3316 (Sec NH); ¹H NMR (300 MHz) (δ , ppm); 7.2-7.4 (m, 5H, Ar-H), 8.7 (s,1H, NH).

Compound 2b: Yield 88%, m. p.178-180°C; IR(KBr) (ν cm⁻¹); 1140-1054 (C-Cl),1470, 1610 (C=C,Ar), 161 5(C=C), 1681 (C=N), 2227 (CN), and 3310 (Sec NH); ¹H NMR (300 MHz) (δ , ppm); 3.76 (3H, s, OCH₃), 7.2-8.4 (m,4H, Ar-H), 8.7 (s,1H, NH).

Compound 2c: Yield 70%, m. p.212-214°C; IR (KBr) (ν cm⁻¹); 1445-1048 (C-Cl), 1462, 1618 (C=C, Ar) 1608(C=C), 1672 (C=N), 2232 (CN), and 3306 (Sec NH), 3512 (OH); ¹H NMR (300 MHz) (δ , ppm); 7.1-7.5 (m,5H, Ar-H), 8.6(s,1H, NH), 10.01(1H, s, OH).

Compound 2d: Yield 81%, m. p.160-162°C; ¹H NMR (300 MHz) (δ , ppm); 7.3-7.3 (m,4H, Ar-H), 8.6(s,1H, NH).

Compound 2e: Yield 76%, m. p.160-162°C; IR (KBr) (ν cm⁻¹); 1138-1041 (C-Cl), 1465, 1622 (C=C,Ar) 1612 (C=C), 1678 (C=N), 2224 (CN), and 3314 (Sec NH).

Compound 2f: Yield 80%, m. p.-208-210°C; ¹H NMR (300 MHz) (δ , ppm); 7.8-8.7 (m,4H, Ar-H), 8.8 (s,1H, NH).

Compound 2g: Yield 84%, m.p.158-160°C; ¹H NMR (300 MHz) (δ , ppm); 7.9-8.8 (m,4H, Ar-H), 8.6 (s,1H, NH).

Compound 2h: Yield 77%, m. p.158-160°C; IR (KBr) (ν cm⁻¹); 1120-1042 (C-Cl), 1455, 1613 (C=C, Ar) 1622 (C=C), 1550 (NO₂), 1663 (C=N), 2235 (CN), and 3327 (Sec NH).

Compound 2i: Yield 73%, m. p. 218-220°C; ¹H NMR (300 MHz) (δ , ppm); 7.7-8.6 (m,4H, Ar-H), 8.4(s,1H, NH), 10.12 (1H, S, OH).

Compound 3a: Yield 65%, m. p.212-214°C; IR(KBr) (ν cm⁻¹); 770 (-Cl), 1405-1020 (C-N), 1460, 1620 (C=C, Ar) 1618 (C=C), 2215(CN), 3130 (Sec NH), 3410 (pri.NH₂) ; ¹H NMR (300 MHz) (δ , ppm); 7.30-8.30 (m,4H, Ar-H), 8.60 (s,2H, NH), 8.40 (s, 2H, -NH₂).

Compound 3b: Yield 68%, m. p.181-183 °C; IR(KBr) (ν cm⁻¹); 1403-1018 (C-N), 1458, 1615 (C=C, Ar) 1620 (C=C), 2220 (CN), 3126 (Sec NH), 3412 (pri.NH₂), 1550 (-NO₂); ¹H NMR (300 MHz) (δ , ppm); 7.32-8.38 (m,4H, Ar-H), 8.46 (s,2H, NH), 8.23 (s, 2H, -NH₂).

Compound 3c: Yield 60%, m. p. 191-193°C; IR(KBr) (ν cm⁻¹); 1406-1022 (C-N), 1462, 1622 (C=C, Ar), 1620 (C=C), 2218(CN), 3133 (Sec NH), 3401 (pri. NH), 3320 (-OH).

Compound 3d: Yield 62%, m .p.224-226°C; IR(KBr) (ν cm⁻¹); 1407-1023 (C-N), 1456, 1624 (C=C, Ar) 1621 (C=C), 2220(CN), 3126 (Sec NH), 3408 (pri. NH), 3316 (-OH).

Compound 4a: Yield 66%, m. p.188-190°C; IR(KBr) (ν cm^{-1}); 778 (-Cl), 1408-1022 (C-N), 1462, 1618 (C=C, Ar) 1620 (C=C), 2216(CN), 3135 (Sec NH), 1552 (-NO₂); ¹H NMR (300 MHz) (δ , ppm); 7.22-8.40 (m,8H, Ar-H), 9.60 (s,2H, NH), 9.13 (s, 1H, -CH).

Compound 4b: Yield 61%, m. p.157-159°C; IR (KBr) (ν cm^{-1}); 1410-1020 (C-N), 1460, 1624 (C=C, Ar) 1621 (C=C), 2220 (CN), 3126 (Sec NH), 3316 (-OH), 1554 (-NO₂); ¹H NMR (300 MHz) (δ , ppm); 7.20-8.38 (m,8H, Ar-H), 9.80 (s,1H, OH), 9.18 (s, 1H, -CH).

RESULTS AND DISCUSSION

The development of efficient and environmentally acceptable synthetic methods is an important task of modern chemistry. Hence we have developed a synthetic protocol for the synthesis of some new biologically active pyrimidine compounds. Pyrimidine compounds have occupied an important position in natural and synthetic organic chemistry, mainly due to their wide range of biological activities.

CONCLUSION

In the present investigation, some new pyrimidine compounds have been synthesized in moderate to good yields. It is observed that yields are better with electron withdrawing groups as compared with electron releasing groups in aldehydes.

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