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Improved Synthesis of Novel 2,4-Diamino-5-furfurylpyrimidine in Presence of Molecular Sieves

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Furfural undergoes base catalyzed condensations with β-ethoxy-propionitrile to give 3-ethoxy-2-(furan-2-ylmethyl)acrylonitrile (**3**), which in turn reacts with methanolic guanidine in the presence of molecular sieves 3A (MS 3A) to give 2,4-diamino-5-furfurylpyrimidine (**4**) in fairly good yields.

Key Words: Furfural, Furfurylpyrimidine, Propionitrile, Molecular sieves.

INTRODUCTION

Pyrimidine also known as *m*-diazine is the parent substance of a large group of heterocyclic compounds, which have attracted much attention for a long time. A number of 2,4-diamino-5-benzylpyrimidines possess marked antibacterial activity[1] as well as non-classical dihydrofolate reductase (DHFR) inhibitors[2,3]. Due to the presence of pyrimidine base in thymine, cytosine and uracil, which are the essential binding blocks of nucleic acid, DNA and RNA, is one of the possible reason for their activity. On the other hand, their antiviral[4,5] anticancer[6] and anti-HIV[7] properties of 5-substituted-2,4-diaminopyrimidine derivatives have been the subject of increasing interest in many years. Even though 2,4-diamino-5-substituted pyrimidine posses these outstanding properties, synthesis of them are limited due to poor yield (12 %)[8]. Therefore development of new methodology to get the desired pyrimidine derivatives in high yields remains desirable. Molecular sieves play a key role not only as a dehydrating agent but also as an acid catalyst[9], as this contains surface Brønsted and Lewis acid centers[10,11]. Herein, we report a short synthetic methodology which will give 2,4-diamino-5-furfurylpyrimuidine in fairly good yields.

EXPERIMENTAL

All the reagents and chemicals were obtained from Aldrich chemicals company (USA) and Merck were used as received. ^{1}H NMR were recorded on a Bruker DPX 300 MHz NMR instrument at ambient temperature in DMSO-d_6. ^{13}C NMR spectra were recorded at 75 MHz spectrometer at ambient temperature. Chemical shift values are reported in parts per million in δ scale using tetramethylsilane (TMS) as

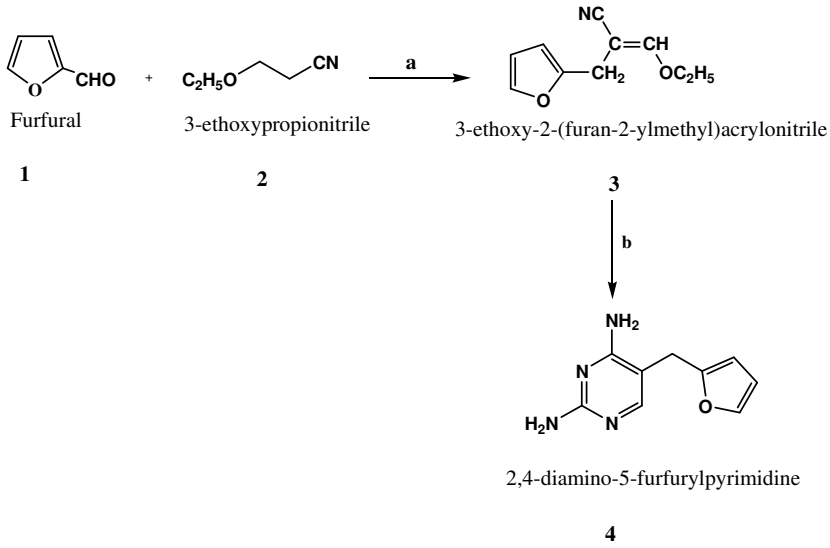
the internal standard. All ^{13}C NMR spectra were recorded with complete proton decupling. Mass spectral data correspond to ESIMS and are given in m/z unit. Melting points were recorded on a SPAC-A Service (India) open capillary melting point apparatus (Laboratory device) and are uncorrected. Infrared spectra were recorded on a JASCO FT-IR Model-410. Spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}. Samples were scanned in KBr discs. Analytical thin layer chromatography was performed on Merck 20 cm × 20 cm silica gel 60-F_{254} plates using appropriate solvents.

Procedure for synthesis of 2,4-diamino-5-furfurylpyrimidine; (4): To a solution of magnesium (3.5 g) and sodium (1.5 g) in methanol (200 mL) there was added β-ethoxypropionitrile (17.0 g; 0.2 mol) and furfural (16.0 g; 0.17 mol). The resulting reaction mixture was refluxed with stirring for 18 h under nitrogen atmosphere. After completion of the reaction (monitored by TLC), the mixture was poured in to ice, the icey mixture was mixed with HCl (150 mL, 2N), the resulting mixture was filtered over Na_2SO_4 and the filtrate was extracted with ether (4 × 50). The ethereal extract was dried and evaporated to give 3-ethoxy-2-(furan-2-ylmethyl) acrylonitrile (**3**) (38 mL; 88 %) as oil. The resulting oil was treated with methanolic guanidine (19.5 g; 0.3 mol) in methanol (250 mL) in the presence of freshly activated molecular sieves **3A** (0.1g per mmol reagent) were added. The resulting reaction mixture was refluxed at 65 °C for 24 h. After completion of the reaction (TLC; $CHCl_3$-CH_3OH (9:1), the MS **3A** was carefully removed by filtration and half the amount of methanol was evaporated by using rotary vacuum evaporator. The resulting concentrated solution was kept for 2 days at room temperature precipitate formed. The crude product was filtered, washed with cold water and recrystallized with hot water to give 2,4-diamino-5-furfurylpyrimidine (35 g; 60 %) as light yellow colour crystals. m.p. 170-172 °C. IR (KBr, cm^{-1}) 3449, 3139, 2882, 2737, 2230, 1628, 1485, 1266, 1147 and 892. ESIMS m/z: 191 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6, ppm); δ 2.1 (s, 5H, CH_2); 3.49 (s, 2H, NH_2); 3.64 (s, 4H, 2 × NH_2); 6.09 (d, J = 21.3 Hz, 3'H); 6.34 (t, J = 1 Hz, 4'H); 7.47 (d, J = 12.3 Hz, 5'H). ^{13}C NMR (75 Mz, DMSO-d_6); 160.5 (C-2); 160.7 (C-4); 103 (C-5); 156 (C-6); 26 (C–CH_2); 153.5(C-2'); 96(C-3'); 110.5(C-4'); 141.5(C-5').

RESULTS AND DISCUSSION

The synthesis of 2,4-diaminopyrimidine could be achieved by various reaction conditions as outlined in (Fig. 1). The synthesis was performed in a stepwise manner involving the isolation of intermediate 3-ethoxy-2-(furan-2-ylmethyl) acrylonitrile (**3**), which are stable, oily in nature, followed it make cyclization with methanolic guanidine in the presence of MS **3A** to give 2,4-diamino-5-furfurylpyrimidne in fairly good yield (60 %). The absence of MS **3A** in the reaction resulted in only a small amount of the desired products (12 %) as reported by McCaustland *et al.*[12], even if the reaction was carried over a long period of time (36 h). To optimize the reaction condition, methanol, ethanol, acetone, benzene and diethyl ether were used

as solvents, with same stochiometry of substrate and reaction time. The enhancement of yield and kinetics of the product (**4**) by addition of **MS 3A** may be due to the removal of H_2O molecule generated during reaction. The results are listed in Table-1.



Reagents and conditions: (a) Na/MeOH, Mg, reflux with stirring for 18 h
(b) Guanidine/MeOH, MS 3A, reflux for 24 h

Fig. 1. Synthesis of 2,4-diamino-5-furfurylpyrimidine

TABLE-1
RESULTS OF VARIOUS REACTION CONDITIONS

No.	Solvent	Molecular sieves 3A	Temp. (°C)	Time (h)	% Yield (isolated)
1	Methanol	+	65	24	60
2	Methanol	–	65	24	12
3	Ethanol	+	65	24	10
4	Ethanol	–	65	24	05
5	Acetone	+	65	24	No reaction
6	Acetone	–	65	24	No reaction
7	Benzene	+	65	24	No reaction
8	Benzene	–	65	24	No reaction
9	Diethyl ether	+	65	24	No reaction
10	Diethyl ether	–	65	24	No reaction

(+) Presence of molecular sieves (3A); (–) Absence of molecular sieves (3A).

Conclusion

The synthesis of 2,4-diamino-5-furfurylpyrimidine was achieved in fairly good yield using MS **3A** as additive. This present methodology indicates new route for obtaining similar compounds and calls for further developments. Further research in the synthesis of derivatives 2,4-diamino-5-furfurylpyrimidine is subject of on-going interest in our laboratory and will be discussed in due course.

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REFERENCES

1. A. Stuart, T. Paterson, B. Roth and E. Aig, *J. Med. Chem*., **26**, 667 (1983).
2. A. Gangjee, O. Adair and S.F. Queener, *Bioorg. Med. Chem*., **9**, 2929 (2001).
3. A. Rosowsky, V. Cody, N. Galitsky, H. Fu, A.T. Papoulis and S.F. Queener, S. F. *J. Med. Chem*., **42**, 4853 (1999).
4. D. Hocková, A. Holý, M. Masojidková, G. Andrei, R. Snoeck, E. De Clercq and J. Balzarini, *Bioorg. Med. Chem*., **12**, 3197 (2004).
5. D. Hocková, A. Holý, M. Masojidková, G. Andrei, R. Snoeck, E. De Clercq and J. Balzarini, *J. Med. Chem*., **46**, 5064 (2003).
6. Y.-L. Huang, C.-F. Lin, Y.-J. Lee, W.-W. Li, T.-C. Chao, V.A. Bacherikov, K.-T. Chen, C.-M. Chen and T.-L. Su, *Bioorg. Med. Chem*., **11**, 145 (2003).
7. A. Rosowsky, R.A. Forsch, C.H. Sibley, C.B. Inderlied and S.F. Queener, *J. Med. Chem*., **47**, 1475 (2004).
8. P. Stenbuck, R. Baltzly and H.M. Hood, *J. Org. Chem*., **28**, 1983 (1963).
9. I. Iovel, L. Golomba, J. Popelis, A. Gaukhman and E. Lukevics, *Chem. Heterocycl. Comp*., **36**, 264 (2000).
10. J. Cejka, H. van Bekkum, A. Corma and F. Schueth, Introduction to Zeolite Science and Practice, Elsevier Publication, USA, pp. 787-789 (2007).
11. S. Friedrich and P. Lothar, *Angew. Chem.*, **14**, 620 (2003).
12. D.J. McCaustland, W.H. Burton, and C.C. Cheng, *J. Heterocycl. Chem*., **8**, 89 (1971).

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