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SOLID PHASE SYNTHESIS OF STRUCTURALLY DIVERSE PYRIMIDO[4,5-d] PYRIMIDINES FOR THE POTENTIAL USE IN COMBINATORIAL CHEMISTRY+

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Abstract : An efficient solid phase synthesis of pyrimido[4,5-d]pyrimidine derivatives is described. Reaction of polymer-bound pyrimidine 1 with urea or thiourea followed by cleavage from the support provided 4-aminopyrimido[4,5-d]pyrimidines 4 and 5 while treatment of 6 with phenyl isocyanate or phenyl isothiocyanate followed by cleavage from resin afforded 3-phenylpyrimido[4,5-d]pyrimidines 9 and 10. © 1999 Elsevier Science Ltd. All rights reserved.

Multiple synthetic technologies on solid support directed towards the generation of diverse, small organic molecules has generated considerable interest as it relates to efficient lead-structure identification[1,2]. Among small organic molecules, nitrogen heterocycles hold a special pharmacophores[3], and as a part of our ongoing programme devoted towards the development of an efficient molecularily diverse heterocyclic systems of biological interest[4-7], we have concentrated our attention on pyrimidine derivatives due to their broad range of useful properties such as antiallergic[8], antitumor[9], antipyratic[10], antiinflammatory[10] and antiparasitic[7] activities.

In an extension of our recent studies[11] towards the generation of diversity on support-bound pyrimidines, we have concentrated on preparation of condensed heterocycles pyrimido[4,5-d]pyrimidines on solid support in which the carbon atoms carring the amino, oxo, thio, anchoring site as well as NH can be utilized as centers to obtain various derivatives of pyrimido[4,5-d]pyrimidines for the potential use in combinatorial chemistry. The details of this study are presented here.

Polymer-bound 2-(alkylthio)-4-aminopyrimidine-5-carbonitrile (1) prepared under standard conditions[11,12], starting from the *Merrifield* resin, on separately treatment with urea and thiourea, produced **2** and **3** as in Scheme 1. Hydrogenation of **2** and **3** over Raney Ni in methanol at 50 psi afforded 4-aminopyrimido[4,5-d]pyrimidine 2(1H)-one (**4**) and 4-aminopyrimido[4,5-d]pyrimidine 2(1H)-thione (**5**) in 76% and 80% yields, respectively.

Hydrolysis of **1** by reported method in alcoholic-KOH gave polymer-bound 2-(alkylthio)-4-aminopyrimidine-5-carboxamide (**6**), in better yield (98%) as obtained earlier by acidic hydrolysis[11], which on treatment separately with phenyl isocyanate and phenyl isothiocyanate produced **7** and **8**. 3-Phenylpyrimido[4,5-d]pyrimidine-1H-2,4-dione (**9**) and 3-phenylpyrimido[4,5-d]pyrimidine-1H-4-one-2-thione (**10**) were obtained from **7** and **8** using similar condition as for **4** and **5**, in 76% and 74% yields, respectively. All the compounds were homogeneous on TLC. The purity was >90% (TLC, NMR)[13].

In conclusion, we report an efficient solid phase method for construction of the pyrimido[4,5-d]pyrimidine framework for other useful synthetic transformations for the potential use in combinatorial chemistry as well as a novel method of cleavage of resin using Raney Ni desulphurization under heterogenous condition.

General Experimental Procedure : Resin **1**, 0.45 meq/g, (1.35 g, 0.6 mmol) and urea or thiourea (10 mmol) were heated on an oil bath at 120°C for 2 hr. The temperature was raised to 140°C and finally the mixture was heated at 200°C for 3 hr. The mixture was then washed successively with DMF (50 ml), CH_2Cl_2 (50 ml) and MeOH (50 ml)

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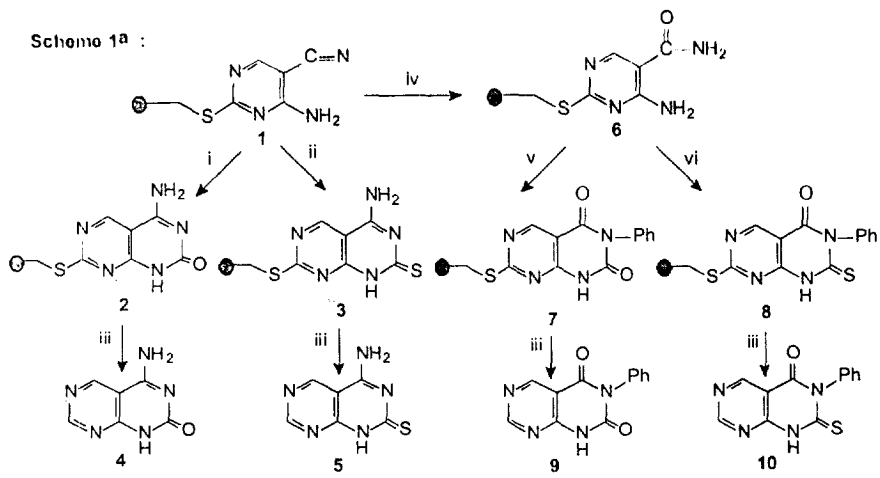
Scheme 1[a] :



[a]**Reagents/conditions** : i, Urea, 120°C; ii, Thiourea, 120°C; iii, Raney Ni/H_2, MeOH, 50 psi; iv, KOH, EtOH, 80°C; v, PhNCO, diphenylether, 259°C; vi, PhNCS, diphenylether, 259°C.

and then dried at 65°C under high vaccum to provide **2** and **3**, respectively. For the synthesis of **7** and **8**, a mixture of resin 6, 0.45 meq/g (1.62 g, 0.72 mmol) and phenyl isocyanate or phenyl isothiocyanate (10 mmol) in diphenylether (50 ml) was refluxed for 8 hr. The resin was then filtered, washed and dried, as described earlier, to provide **7** and **8** respectively. The resin-bound compounds were characterized by IR spectroscopy and the peaks were in agreement with the chemical structure[14]. The resulting resins **2,3** and **7,8** were then hydrogenated separately using Raney Ni in MeOH (30 ml) as solvent for 12 hr and then filtered under hot conditions. The filtrate was then concentrated to provide the respective compounds **4** & **5** and **9** & **10** in 74-80% yield.

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13. **4** IR : 3420, 1682, 1652, 1216 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.83 (s, 1H), 8.26 (s, 1H), 4.9 (bs, 2H, NH_2); MS m/z : 149 (M^+), **5** IR : 3420, 1650, 1218 cm^{-1}; ^1H NMR (DMSO-d_6) : δ 8.76 (s, 1H), 8.31 (s, 1H), 5.2 (bs, 2H, NH_2); MS m/z : 165 (M^+), **9** IR : 3022, 1676, 1650, 1216 cm^{-1} ^1H NMR (DMSO-d_6) : δ 8.93 (s, 1H), 8.58 (s, 1H), 7.37-7.26 (m, 3H), 7.09-7.02 (m, 2H); MS m/z : 240 (M^+), **10** IR : 3030, 1680, 1652, 1216 cm^{-1} ; ^1H NMR (DMSO-d_6) : δ 8.82 (s, 1H), 8.61 (s, 1H), 7.31-7.25 (m, 3H), 7.1-7.0 (m, 2H); MS m/z: 256 (M^+).
14. **2** IR: 3400, 1678, 1650 cm^{-1}; **3** IR: 3410, 1650 cm^{-1}; **7** IR: 3010, 1670, 1648 cm^{-1}; **8** IR: 3020, 1676, 1650 cm^{-1}.