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Research Article

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Microwave Assisted Solid Phase Synthesis of Trisubstituted Pyrimidines

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ABSTRACT

Trisubstituted pyrimidines were synthesised using 2% butanediol dimethacrylate cross linked chloromethyl polystyrene. The polymer was reacted with guanidine and the resulted guanidine functionalised resin was treated with 2-(1-ethoxyethylidene)malononitrile form a polymer bound 2,4-diaminopyrimidine-5-carbonitrile. The pyrimidine nucleus was then detached from the resin using TFA cleavage. The product was isolated with good yield. The reaction was also carried out under microwave reaction conditions and yield was found to be considerably enhanced with significant decrease in the total reaction time. The guanidine functionalised resin was treated with ethylcyano actate/malononitrile to afford 4,6-diamino pyrimidinone and 2,4,6-triaminopyrimidine derivatives. The products were characterized by IR, NMR and HRMS analysis.

Keywords: Solid phase synthesis; chlomethyl polystyrene; substituted pyrimidines

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INTRODUCTION

Many biologically active compounds contain nitrogen heterocyclic systems and the methods for the synthesis of functionalized heterocycles are of great importance in medicinal and pharmaceutical chemistry [1,2]. Solid phase organic synthesis receives much attention for the rapid synthesis of libraries of organic compounds as drug candidates [3,4]. The main advantage of solid phase organic synthesis includes simple reaction work-up, rapid synthesis by avoiding chromatographic purification of intermediates and high yield by using excess of the reagent or substrate. Since the intermediates are bound to the polymer separation and purification can be effected by simple filtration and washing. The reactions can be driven to completion by using excess of reagents or substrates leading to high product yield and the by-products can be removed by simple filtration [5]. The products can be cleaved from the solid support by simple cleavage mechanisms and intermediate purification procedures can be avoided. The nitrogenous bases present in nucleic acid are pyrimidine or fused pyrimidine derivatives and many natural products contain pyrimidine nucleus. Many pyrimidine containing compounds are important drugs and agricultural chemicals and exhibit antibacterial, antifungal, antiviral, tuberculostatic, anti-inflammatory and anticancer properties [6-8]. Antiviral drugs like Idoxuridine (i), Trifluridine, Zalcitabine and Zidovudine (ii) belong to pyrimidine family. Solid phase synthesis under microwave irradiation is a newly developing as well as an interesting field. Present paper describes the conventional and microwave assisted solid phase synthesis of trisubstituted pyrimidines using 2% butanediol dimethacrylate cross linked polystyrene support.

METHODOLOGY

Synthesis of Polymer Support

A homogeneous mixture of styrene (98 mol%), BDDMA (2 mol%), toluene (20 mL) and benzoyl peroxide (500 mg) were suspended in a 1% aqueous solution of polyvinyl alcohol (175 mL) and kept mechanically stirred at 600 rpm at a temperature of 85°C. After 6 h the beaded resin was filtered, washed and subjected to Soxhlet extraction with acetone followed by methanol to remove linear polymers and low molecular weight products. The beads were meshed to 200–400 range.

Functionalisation of Polymer Support

The BDDMA cross linked polymer (1g) was refluxed with chloromethyl methyl ether (6 mL) and freshly prepared $ZnCl_2$ in THF (0.3 mL) at 50°C for 4 h. After reaction the resin was filtered, washed with THF, THF/H2O and was subjected to Soxhlet extraction with THF. The chlorine capacity of the resulted resin was estimated by pyridine fusion method and was found to be 4.0 mmol/g [9].

Solid Phase Synthesis of 2,4-Diaminopyrimidine-5-Carbonitrile (4)

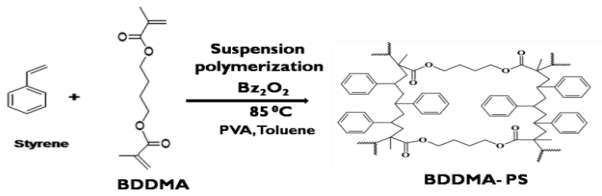
Chloromethyl polystyrene 1 (250 mg, 4.0 mmol Cl/g) swelled in NMP (10 mL) was heated with guanidine hydrochloride (2 mmol, 191.06 mg) at 85°C for 12 h in presence of Cs_2CO_3 (400 mg) [9]. The resin was then filtered, washed several times with NMP, NMP:H_2O (1:1), methanol and DCM and dried. of the resulted resin 2 (250 mg) was refluxed for 8 h with ethanolic solution of 2-(1-ethoxyethylidene)malononitrile (488.52 mg, 4 mmol) in presence of triethylamine (0.4 mL). The resulted polymer bound pyrimidine derivative 3 was filtered, washed with methanol and DCM and dried. In the final step the resin 3 (250 mg) was mixed with TFA/DCM (1:9, 15 mL) and stirred for 1 h at room temperature. The spent resin was filtered off, washed with DCM and methanol and the filtrate was collected and evaporated to get a solid product. The solid product was then recrystallised from methanol to get pure 2,4-diaminopyrimidine-5-carbonitrile with a yield of 79%.

Microwave Assisted solid Phase Synthesis of 2,4-Diaminopyrimidine-5-Carbonitrile (4)

Chloromethyl polystyrene 1 (250 mg, 4 mmol Cl/g) swelled in NMP was treated with guanidine hydrochloride (2 mmol, 191.06 mg) at 85°C for 10 min under microwave irradiation in presence of Cs_2CO_3 (400 mg). Then the resin was filtered, washed several times with NMP, NMP:H_2O (1:1) mixture, methanol and DCM and dried. 250 mg of the resulted resin 2 was treated with ethanolic solution of 2-(1-ethoxyethylidene)malononitrile (488.52 mg, 4 mmol) under microwave irradiation for 20 min in presence of triethylamine (0.4 mL). The resulted resin 3 was filtered, washed with methanol and DCM and dried. In the final step 250 mg of the resin 3 was mixed with 15 mL TFA/DCM mixture (1:9) and stirred for 10 min under microwave irradiation. The resulted resin was filtered, washed with DCM and methanol. The filtrate was collected and evaporated to get a solid product. The solid product was then recrystallised from methanol to get pure 2,4-diaminopyrimidine-5-carbonitrile with an yield of 90%.

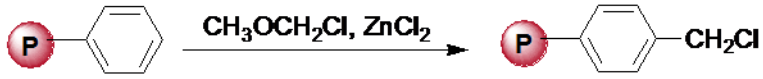
RESULTS AND DISCUSSIONS

The BDDMA cross linked polystyrene support was prepared by the radical initiated suspension polymerisation of monomers styrene and BDDMA (Scheme 1).



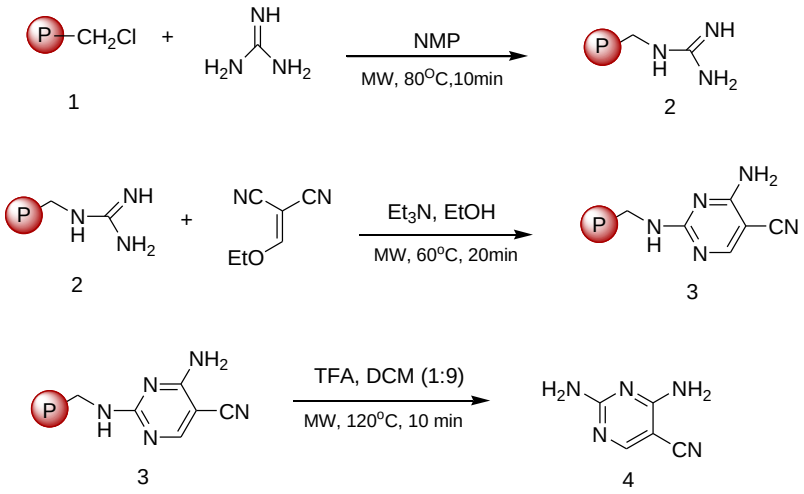
Scheme 1: Synthesis of BDDMA cross linked polystyrene support

The IR spectrum of resin showed a sharp band 1720 cm^{-1} corresponding to the carbonyl group of the BDDMA cross linker. The cross linked polystyrene was functionalised with chloromethyl groups via Friedel–Crafts chloromethylation reaction using chloromethyl methyl ether in presence of anhydrous $ZnCl_2$ as catalyst (Scheme 2). The functionalisation was confirmed from IR spectrum of the chloromethylated resin which showed a characteristic C–Cl stretching band at 680 cm^{-1}.



Scheme 2: Chloromethylation of BDDMA cross linked polystyrene

To synthesise 2,4-diaminopyrimidine-5-carbonitrile with 2% of BDDMA cross linked chloromethyl polystyrene resin having a chlorine loading capacity of 4.0 mmol/g as the solid support, at first, the N-C-N part of the pyrimidine ring was immobilised on the polymer support 1 using guanidine hydrochloride in presence of Cs_2CO_3 as the base in NMP solvent. The completion of reaction required a time of 12 h. The resulted guanidine immobilised resin 2 was heated with 2-(1-ethoxyethylidene) malononitrile under basic condition (Et3N) in ethanol for 8 h to afford the resin bound pyrimidine derivative 5 (Scheme 3). Finally the product 2,4-diaminopyrimidine-5-carbonitrile 6 was cleaved from resin 5 using 90% TFA in DCM . For this the resin 5 was treated with TFA in DCM for 1 h with constant stirring. The product 2,4-diaminopyrimidine-5-carbonitrile 6 was obtained in pure form with 79% yield by recrystallising from methanol.



Scheme 3: Microwave assisted solid phase synthesis of 2,4-diaminopyrimidine-5-carbonitrile

Progress of the synthesis was monitored by FTIR spectral analysis. The replacement of Cl atoms present in chloromethylated resin 1 by guanidine was confirmed from the absence of C–Cl stretching at 680 cm-1and presence of new bands at 3470 and 3380 cm^{-1} corresponding to NH stretching in guanidine immobilised resin 2. In the second step reaction of resin 2 with ethoxyethylidenemalononitrile took place which was confirmed by the appearance of a band at 2188 cm^{-1} due to C≡N stretching of cyanide group present in resin 3. In the final step the product 2,4-diaminopyrimidine-5-carbonitrile was cleaved from the polymer support using 90% TFA in DCM and the spent polymer support was filtered off and evaporation of the solvent and further recrystallisation from methanol afforded the 2,4-diaminopyrimidine-5-carbonitrile in 79% yield.

The product 2,4-diaminopyrimidine-5-carbonitrile was characterized by IR, NMR and HRMS analysis (Figures 1-3). The IR spectrum of compound shows bands at 2188 (υ C≡N), 3480 (υ NH) and 3080 (υ CH) cm^{-1}. HRMS spectum shows an [M+H] peak at 136.0778 indicates the formation of product. In 1H NMR spectrum appearance of singlets at δ 6.9 ppm corresponds to four NH2 protons and δ 8.05 ppm due to the aromatic proton confirms the formation of product. The 13C NMR spectrum also supports the structure of the product from the following peaks at δ 83.0 ppm (C5), 117.0 ppm (C ≡N), 161.3 ppm (C6), 166.6 ppm and 167.2 ppm (C2 & C4) (Figure 1).

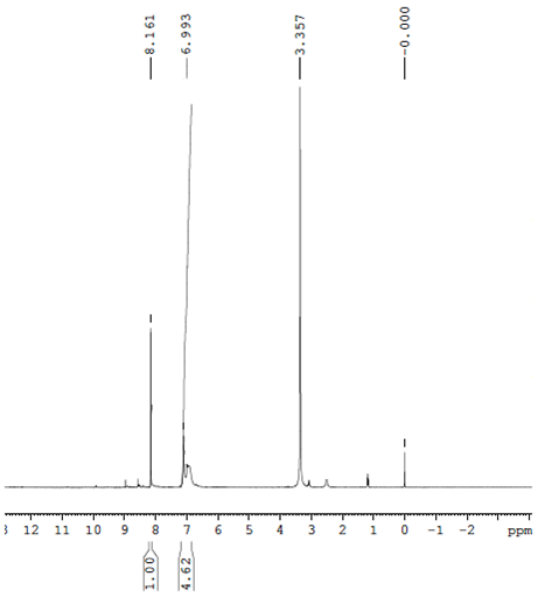


Figure 1: ^{1}HNMR spectrum of the synthesised 2,4-diaminopyrimidine-5-carbonitrile

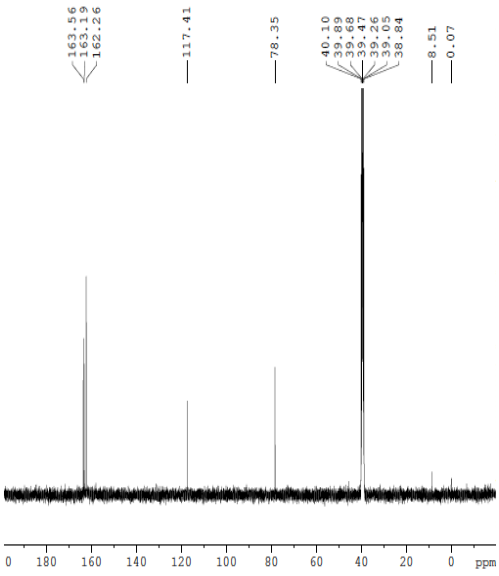


Figure 2: 13CNMR spectrum of the synthesised 2,4-diaminopyrimidine-5-carbonitrile

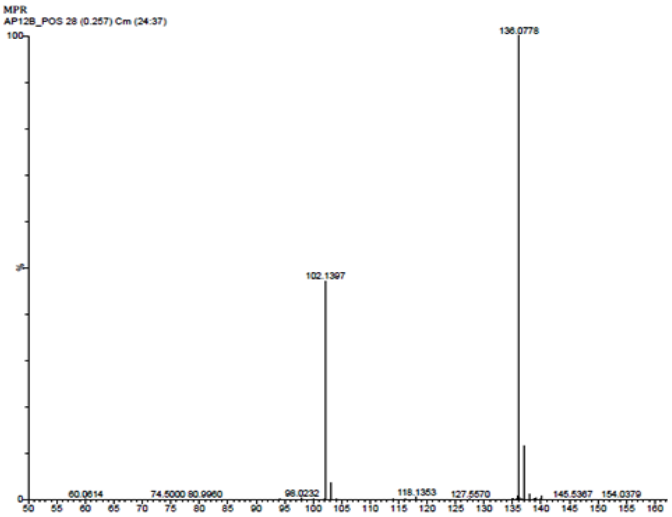
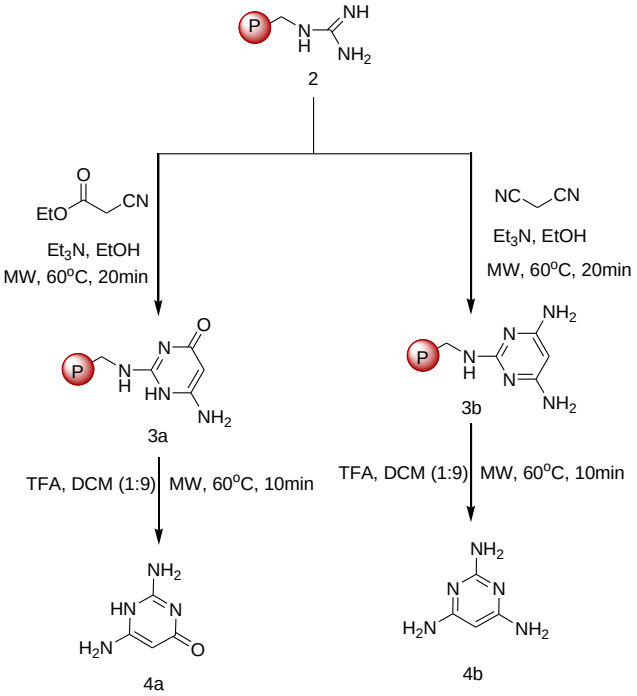


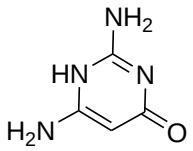
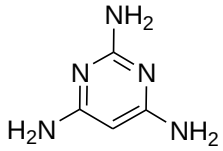
Figure 3: HRMS spectum of 2,4-diaminopyrimidine-5-carbonitrile

The solid phase synthesis of 2,4-diaminopyrimidine-5-carbonitrile was also carried out under microwave irradiation condition and was compared with the existing conventional solid phase synthesis, it reveals the following features. (i) The reaction time could be reduced considerably from hours to minutes. The time needed for the completion of first step of guanidine immobilisation could be reduced from 12 h to 10 min and the time required for second step, i.e., the pyrimidine core formation step was reduced from 8 h to 20 min. The TFA cleavage was finished with time period 10 min under microwave irradiation instead of 1 h. Thus overall time required for the completion of the reaction was reduced from 21 h to 40 min. (ii) The product yield was found to be increased from 79% to 90%.

Using the above mentioned synthetic strategy 4,6-diamino pyrimidinone (89% yield) and 2,4,6-triaminopyrimidine (92% yield) were synthesised by replacing ethoxyethylidenemalononitrile by ethylcyano actate and malononitrile (Scheme 4) and are characterised (Figures 2 and 3).



Scheme 4: Microwave assisted solid phase synthesis of trisubstituted pyrimidines

Compound	Characterisation
4,6-Diamino pyrimidinone (**4a**)  Obtained as pale yellow solid (89% yield).	FTIR: 3463, 3390 cm^{-1} (υ_{NH}) and 1698 cm^{-1} (υ_{CO}). ^{1}HNMR (400 MHz, DMSO-d6) δ 6.9 ppm (S,4H), δ 8.1 ppm (S,1H), δ 5.4 ppm (S,1H). ^{13}CNMR (100 MHz) 154.4 ppm (C2), 178.9 ppm (C4), 94.8 ppm (C5) and 167.5 ppm (C6). [M+H]=127.4751.
2,4,6-Triaminopyrimidine (**4b**)  Obtained as yellow solid with 92% yield.	FTIR: 3446, 3387 cm^{-1} (υ_{NH}). ^{1}HNMR (400 MHz, DMSO-d6) δ 6.9 ppm (S, 6H), δ 5.8 ppm (S,1H). ^{13}CNMR (100 MHz) 162.4 ppm (C2), 165.9 ppm (C4), 99.1 ppm (C5) and 165.9 ppm (C6). [M+H]=126.3741.

CONCLUSIONS

In this work, we successfully develop complete microwave assisted protocols for the synthesis of pyrimidine derivatives. Here solid phase synthesis was used for the synthesis of 2,4-diaminopyrimidine-5-carbonitrile. Next microwave assisted solid phase synthesis of 2,4-diaminopyrimidine-5-carbonitrile was developed. Similary 4,6-diamino pyrimidinone and 2,4,6-triaminopyrimidine were synthesised. Application of microwave irradiation to each step of the reaction, i.e., guanidine immobilisation, pyrimidine ring formation and cleavage of resin, reduced the reaction time considerably. The time required for the completion of the reaction was reduced from 21 hours to 40 minutes. Thus the increased reaction time of conventional solid phase synthesis was considerably reduced with the microwave assisted solid phase synthesis.

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