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POLYANILINE SULFATE SALT MEDIATED ONE-POT THREE-COMPONENT SYNTHESIS OF TRIHETEROCYCLIC 4*H*-PYRIMIDO[2,1-*B*]BENZOTHIAZOLE DERIVATIVES

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Abstract: An alternative synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazole derivatives has been developed by one pot three-component condensation reaction of 2-aminobenzothiazole with substituted benzaldehydes and *β*-dicarbonyl derivatives using polyaniline sulfate salt (PASS) in good to excellent yields.

Key words: Polyaniline sulfate salt, multicomponent condensation, pyrimidobenzothaizole.

Introduction:

Acid catalysts are often being used in organic syntheses and industrial processes. For example, sulfuric acid, fluorohydric acids are used in alkylation, esterification, hydrolysis reactions, etc.[i] However, these acid catalysts are toxic, corrosive and in addition, are hard to remove from the reaction medium. The environmental care is one of the worldwide increasing problems. The replacement of environmental hazardous catalysts existing processes, by the use of solid acid catalysts such as zeolites, alumina, resins, etc., is one of the innovative trends. Each catalyst has its own advantages and disadvantages. It is always interesting to develop a new environmental benign catalyst for organic transformations. Polyaniline supported metal catalysts in organic syntheses are reported in literature.[ii] Recently reported several organic transformations using polyaniline salts as polymer based solid acid catalyst (Fig.1) in organic solvents.[iii]

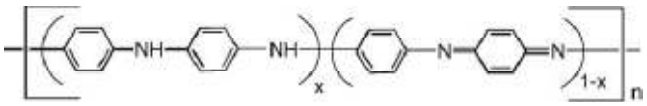


Fig. 1

Bicyclic 3,4-dihydropyrimidin-2(1*H*)-one such as 4*H*-pyrimido[2,1-*b*]benzothiazoles, thiazdopyrimidines and imidazopyrimidine, which have potent vasorelaxant activity, these are prepared in two steps by Atwal modification of Biginelli reaction [iv] and single step in ionic liquids.[v] Biginelli condensation reaction is a three-component condensation of an aldehydes, a urea or thiourea and *β*-carbonyl compounds under acidic conditions in ethanol.[vi]

Compounds having benzothiazole moiety posses wide variety of biological activities such as anticonvulsant,[vii] antitumor,[viii] anti-inflammatory [ix] and antitubercular [x], also act as chemo sensitizer in chemotherapy and neuroprotectant-cerebral antischemic agent.[xi] We now report an alternative synthetic route to 4*H*-pyrimido[2,1-*b*]benzothiazole derivatives (**4a-j**) utilizing polyaniline salts as a catalyst by the condensation reaction of 2-aminobenzothiazole (**1**) with substituted benzaldehyde (**2a-f**) and *β*-dicarbonyl derivatives (**3a-e**) in ethylene glycol (Scheme 1).

Material and Methods

Melting points were measured with a Fischer-Johns melting point apparatus and are uncorrected. IR spectra were recorded as neat liquids or KBr pellets and absorptions are reported in cm^{-1}. NMR spectra were recorded on 300 (Bruker) and 500 MHz (Varian) spectrometers. ^{13}C NMR spectra were recorded on 75 and 125 MHz spectrometers. Reagents and all solvents were analytically pure and were used without further purification. All the experiments were monitored by analytical thin layer chromatography (TLC) performed on silica gel GF254 pre-coated plates. Silica gel finer than 200 mesh was used for column chromatography.

Preparation of Polyaniline-Sulfate Salt by the aqueous-polymerization pathway using sulfuric acid:

Aniline (2.3 mL) and sulfuric acid (9 mL) were dissolved in 90 mL of distilled water containing 5.71 g of ammonium persulfate was added drop wise to the above solution over a period of approximately 20 minutes. The reaction was allowed to proceed for 4 h. The precipitate was separated from the reaction mixture and washed three times with 300 mL water followed by 300 mL of acetone. The powder was dried at 100 ^oC till the constant mass was reached.[xii]

General Synthesis

General experimental procedure for the preparation of compounds (4a-j):

2-Aminobezothiazole (1 mmol), benzaldehyde (2.0 mmol) and ethyl acetoacetate (2.0 mmol), ethylene glycol (5 mL) and polyaniline salts (2.4 wt%) were added at room temperature and heated at 120 ^oC for 1-2 h. Progress of the reaction was monitored by TLC (ethyl acetate: hexane 3:7). After completion of the reaction, reaction mixture was allowed to cool, diluted with water and extracted with ethyl acetate. Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (ethyl acetate: hexane 3:7).

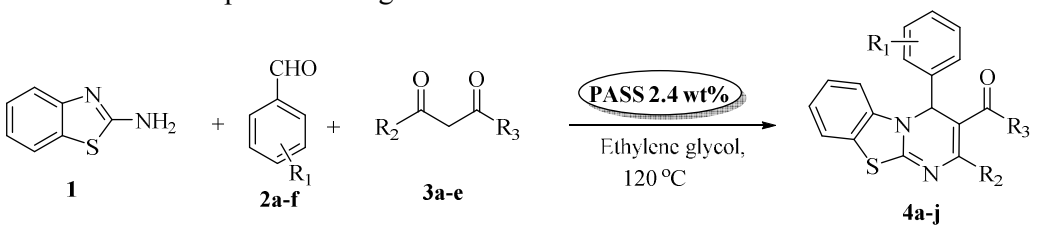
Representative Spectral data:

Ethyl-2-methyl-4-(phenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate **(4a):** Yield: 80%, mp 176-178 ^oC (Reported[xiii] mp 177-179 ^oC). IR: ν_{max} 2930, 1675, 1585, 1242, 1100, 745, 705, 635 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.30 (t, 3H, CH_3), 2.40 (s, 3H , CH_3), 4.15 (q, 2H, OCH_2), 6.32 (s, 1H, CH), 7.02-7.10 (m, 2H, Ar-H), 7.15-7.25 (m, 4H, Ar-H), 7.35-7.45 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 14.20, 23.55, 57.60, 61.10, 103.00, 110.93, 122.00, 123.80, 126.00, 128.25, 128.510, 128.63, 137.80, 141.20, 147.20, 154.45, 155.60, 163.60, 166.40. MS $(ESI)^+$: m/z= 351 $[M+H]^+$. ***3,3-Dimethyl-12-phenyl-2,3,4,12-tetrahydro-1H-benzo [4,5] [1,3] thiazolo [2,3-b]quinazolin-1(2H)-one*** **(4e):** Yield: 70% , mp. 203-205 (Reported[xiii] mp 205-207 ^oC). IR: ν_{max} 2935, 2875, 1660, 1610, 1470, 1265, 1130, 985, 615 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.90 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.20 (d, *J*=8.0 Hz, 2H, CH_2), 2.45 (s, 2H, CH_2), 6.42 (s, 1H, CH), 7.00 (d, *J*=8.40 Hz, 1H, Ar-H), 7.12-7.16 (m, 2H, Ar-H), 7.18-7.25

(m, 3H, Ar-H), 7.35 (d, *J*=8.0 Hz, 2H, Ar-H), 7.45 (d, *J*=7.15 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 27.20, 32.55, 45.20, 50.80, 56.00, 110.30, 112.20, 122.00, 124.10, 126.80, 128.10, 128.60, 138.20, 140.55, 158.45, 165.55; 195.30; MS $(ESI)^+$: m/z= 361$[M+H]^+$. ***Ethyl-2-methyl-4-(4-nitrophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate*** **(4g):** Yield: 68%, mp. 157-158 °C (Reported[xiii] mp 156-158 °C). IR:ν_{max} 2925, 1670, 1550, 1335, 1245, 1110, 1095, 983 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.20 (q, 2H, OCH_2), 6.58 (s, 1H, CH), 7.00 (d, *J*=8.00 Hz, 1H, Ar-H), 7.15 (t, 1H, Ar-H), 7.22 (t, 1H, Ar-H), 7.46 (d, *J*=8.00 Hz, 1H, Ar-H), 7.60 (d, *J*= 8.20 Hz, 2H, Ar-H), 8.10 (d, *J*=8.25 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 14.32, 24.00, 57.00, 60.35, 102.00, 111.76, 122.40, 123.70, 123.90, 124.32, 126.78, 127.90, 137.40, 147.88, 155.80, 163.50, 166.20; MS $(ESI)^+$: m/z= 396$[M+H]^+$. ***Ethyl-2-methyl-4-(4-methoxyphenyl)-4H-pyrimido[2,1-b] [1,3] benzothiazole-3-carboxylate*** **(4h):** Yield: 80%, mp.141-142 °C (Reported[xiii] mp 141-144 °C). IR: ν_{max} 2900, 1680, 1585, 1470, 1255, 1206, 1090, 985, 740 cm^{-1} . ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.20 (q, 2H, OCH_2), 6.35 (s, 1H, CH), 7.02-7.10 (m, 1H, Ar-H), 7.20-7.30 (m, 3H, Ar-H), 7.36-7.55 (m, 3H, Ar-H), 8.10 (d, *J*=7.00 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 23.0, 57.50, 60.00, 60.55, 65.55, 102.40, 111.70, 120.68, 122.00, 124.00, 127.00, 128.00, 128.40, 129.46, 132.50, 141.00, 155.00, 163.50, 166.20; MS $(ESI)^+$: m/z= 381 $[M+H]^+$.

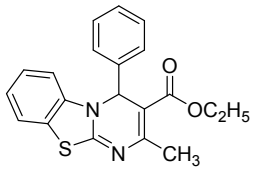
Results and Discussion

Initially, a model reaction was examined using 2-aminobenzothiazole (**1**), benzaldehyde (**2**) and ethyl acetoacetate (**3**) in the presence of polyaniline salt (2.4 wt%) in ethylene glycol as solvent (Scheme 1). After 2 h 80% of 4*H*-pyrimido[2,1-*b*]benzothiazole (**4**) product was isolated. When the amount of polyaniline salt is increased to 4.8 wt%, the yield was slightly increased from 80% to 82% with various *β*-dicarbonyl derivatives, and several derivatives of **4a-j** were synthesized in good to excellent yields with 2.4 wt% polyaniline salt (Scheme 1). The structure of the product **4a-j** was established from their spectral data IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopic analyses. The formation of compound **4a** was evident from the appearance of $[M+H]^+$ peak at *m/z* 351 in mass spectrum $(ESI)^+$ and the appearance of characteristic methine proton as singlet at δ 6.32 in ^{1}H NMR.

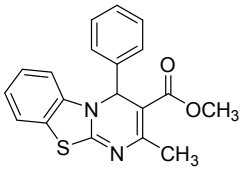


1 **2a-f** **3a-e** **4a-j**

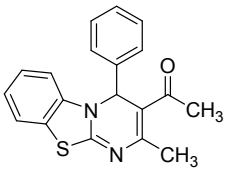
Scheme 1



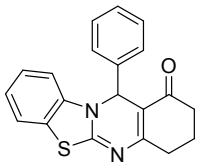
4a, 80%, m.p. 176-178 °C



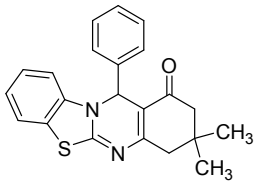
4b, 76%, m.p. 145-147 °C



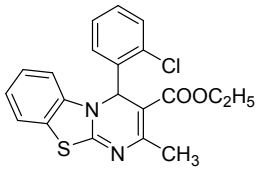
4c, 70%, m.p. 136-138 °C



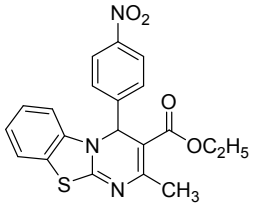
4d, 74%, m.p. 216-217 °C



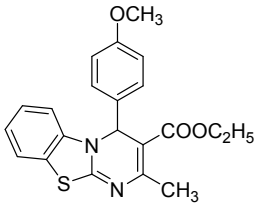
4e, 70%, m.p. 203-205 °C



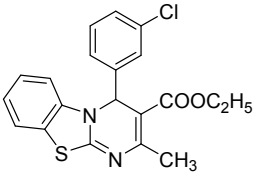
4f, 72%, m.p. 125-127 °C



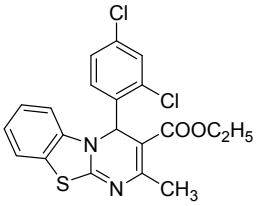
4g, 68%, m.p. 157-158 °C



4h, 80%, m.p. 141-142 °C



4i, 70%, Liquid



4j, 76%, m.p. 131-133 °C

In conclusion, we have developed an alternative approach for the synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazole derivatives using 2.4 wt% of polyaniline sulfate salt in good to excellent yields and short reaction times.

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