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ARTICLE

Silicotungstic Acid Catalyzed Microwave Assisted Synthesis of Fused 4*H*-Pyrimido[2,1-*b*]thiazoles and 4*H*-Pyrimido[2,1-*b*]benzothiazoles under Solvent-Free Conditions

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Asian Journal of Organic & Medicinal Chemistry

Volume: 5 Year: 2020
Issue: 1 Month: January–March
pp: 62–67
DOI: https://doi.org/10.14233/ajomc.2020.AJOMC-P236

Received: 11 October 2019
Accepted: 12 February 2020
Published: 5 May 2020

ABSTRACT

The silicotungstic acid catalyzed microwave assisted synthesis of substituted 4*H*-pyrimido[2,1-*b*]thiazole and 4*H*-pyrimido[2,1-*b*]benzothiazole derivatives was achieved by one-pot multi-component reaction of 2-aminothiazole or 2-aminobenzthiazole, aldehyde and ethyl acetoacetate under solvent-free condition. A simple, rapid and environmental friendly protocol, good yields and easy work-up are some advantages of this protocol. The structures of the synthesized compounds were established by FT-IR, ^{1}H NMR and mass spectral data.

KEYWORDS

Silicotungstic acid, Pyrimido[2,1-*b*]thiazole, Microwave, Solvent-free, Multicomponent.

INTRODUCTION

The fused heterocyclic compounds attracted much attention in the field of medicinal chemistry because of their significant contribution in the biological profile of drug. Multicomponent reactions (MCRs) as a powerful tool have been widely utilized in organic synthesis, combinatorial and medicinal chemistry due to their simplicity and flexibility, good yield, high variability and selectivity, greater atom economy, energy savings and reduced waste. In the past decades, MCRs were used to construct a number of interesting heterocyclic scaffolds having 'drug-like' properties [1].

Fused heterocyclic compounds comprising nitrogen and sulphur are important because of their interesting pharmacological properties [2]. Among these compounds benzothiazoles and pyrimido[2,1-*b*]benzothiazoles have enticed considerable attention. Some of these compounds have different biological properties such as antiviral [3], antitumor [4], anti-inflammatory [5], antiallergic [6], antimicrobial [7], anticonvulsant [8], antiproliferative [9] and antifungal [10].

Pyrimido[2,1-*b*]benzothiazole derivatives were synthesized *via* multicomponent reactions between 2-amino benzothiazole, aromatic aldehydes and β-ketoesters [11]. Previously, this reaction has been catalyzed by iron fluoride [12], acetic acid

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[13], pyridine [7], chitosan [14], aluminium trichloride [15], 1,1,3,3-*N,N,N',N'*-tetramethylguanidinium tri-fluoroacetate (TMGT) [16], tetrabutylammonium hydrogen sulphate (TBAHS) [17], *N*-sulfonic acid modified poly(styrene-maleic anhydride) (SMI-SO_3H) and Fe_3O_4@nano-cellulose/TiCl [18]. Several reactions possess advantages over traditional reactions in organic solvents such as solvent-free multicomponent reactions with recyclable heterogeneous catalysts decrease the consumption of hazardous solvents and utilize scaled-down reaction vessels. However some of the reported protocols have harsh reaction conditions with prolonged reaction times.

The usage of solid acids as heterogeneous catalyst has received much attention in different areas of organic synthesis [19]. Heteropolyacids (HPAs) have numerous advantages, comprising high flexibility on modification of the acid strength, ease of handling, experimental simplicity, non-toxicity and environmental compatibility [20]. They are known to have a strong Brønsted acidity and found to be very efficient in Lewis acid catalyzed conventional reactions. Thus, the use of HPAs as a catalyst makes the process convenient and environmentally benign. HPAs found to possess outstanding catalytic properties in the dehydration of diols, rearrangements, tetrahydropyranylation of alcohols, Friedel-Craft alkylation, Prins reaction, synthesis of dihydroquinolines, pyrimidine synthesis, Biginelli reaction and Dakin-West reaction [21].

In a view of unlimited importance of pyrimidothiazole derivatives, we herein report a simple, rapid and high yielding microwave assisted one-pot multicomponent reaction protocol for the synthesis of pyrimidothiazole and pyrimidobenzothiazole derivatives employing environmentally benign silicotungstic acid ($H_4[SiW_{12}O_{40}]$) as a heterogeneous catalyst under solvent-free conditions (**Scheme-I**).

EXPERIMENTAL

All the chemicals and solvents used were of analytical grade and used without purification. All the reactions were monitored by thin layer chromatography, (TLC silica gel 60 F_{254} by Merck) and were visualized under a UV lamp and using iodine vapours. The melting points were ascertained with a digital thermometer and are uncorrected. IR spectra were recorded on FT-IR spectrometer (Perkin Elmer). ^{1}H NMR spectra were recorded on Bruker DRX FT spectrometer at 400 MHz using acetone-d_6 and $CDCl_3$ as a solvent. Chemical shift values recorded are mentioned in parts per million (ppm) and observed downfield from TMS, while coupling constants (*J*) are referred to in hertz (Hz).

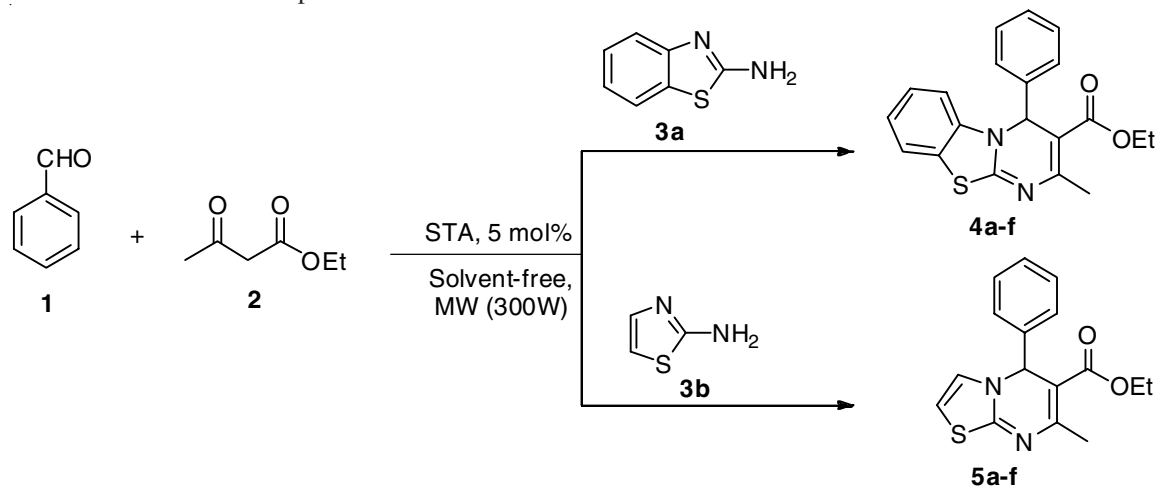
General procedure for the synthesis of pyrimidothiazoles and pyrimidobenzothiazoles (4a-f/5a-f): A mixture of 2-amino benzthiazole or 2-aminothiazole (1 mmol), appropriate aldehyde (1 mmol), ethyl acetoacetate (1 mmol) and silicotungstic acid (5 mol%) was placed in a microwave vial with snap on cap. The reaction mixture was subjected to microwave irradiation for appropriate time at 300 W in a conventional microwave oven. After completion of reaction (TLC), the reaction mixture was cooled to room temperature and ethanol (2 mL) added to it. Poured the mixture into ice cold water and precipitate obtained was filtered, dried and purified by column chromatography using petroleum ether:ethyl acetate as eluent (90:10) (**Scheme-I**).

Spectral data of the synthesized compounds

Ethyl-2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (4a): Pale yellow solid; m.p.: 176-178 °C; IR (KBr, ν_{max}, cm^{-1}): 1692, 1591, 1466, 1248, 745; ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.68 (dd, *J* = 8, 1.2 Hz, 1H, ArH), 7.53-7.50 (m, 2H, ArH), 7.42 (dd, *J* = 8, 1.2 Hz, 1H, ArH), 7.31-7.36 (m, 3H, ArH), 7.22-7.27 (m, 2H, ArH), 6.49 (s, 1H-CH-), 4.05 (q, *J* = 7.2 Hz, 2H,-CH_2), 2.36 (s, 3H,-CH_3), 1.22 (t, *J* = 7.2 Hz, 3H, -CH_3); LCMS (ESI): 351.08 (M+1).

Ethyl-4-(4-chlorophenyl)-2-methyl-4*H*-benzo[4,5]-thiazolo[3,2-*a*]pyrimidine-3-carboxylate (4b): Pale yellow solid; m.p.: 88-90 °C; IR (KBr, ν_{max}, cm^{-1}): 1695, 1590, 1468, 1250, 744; ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.66 (dd, *J* = 8, 1.2 Hz, 1H, ArH), 7.48 (d, *J* = 7.6 Hz, 2H, ArH), 7.38-7.34 (m, 3H, ArH), 7.30 (m, 1H, ArH), 7.25 (m, 1H, ArH), 6.42 (s, 1H, -CH-), 4.08 (q, *J* = 7.2 Hz, 2H, -CH_2-), 2.29 (s, 3H,- CH_3), 1.21 (t, *J* = 7.2 Hz, 3H, -CH_3); LCMS (ESI): 385.79 (M+1).

Ethyl-2-methyl-4-(4-nitrophenyl)-4*H*-benzo[4,5]-thiazolo[3,2-*a*]pyrimidine-3-carboxylate (4c): Brown solid; m.p.: 169-171 °C; IR (KBr, ν_{max}, cm^{-1}): 1702, 1596, 1465, 1251, 746; ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.22 (d, *J* = 8.2 Hz, 2H, ArH), 7.68 (dd, *J* = 8.0, 1.2 Hz, 1H, ArH), 7.60 (d, *J* = 8.2Hz, 2H, ArH), 7.38-7.35 (m, 2H, ArH), 7.19 (m, 1H, ArH),



Scheme-I: Heteropolyacid catalysed MW assisted synthesis of pyrimidobenzothiazoles

6.48 (s, 1H, -CH-), 4.08 (q, *J* = 7.2 Hz, 2H, -CH_2-), 2.35 (s, 3H, -CH_3), 1.22 (t, *J* = 7.2 Hz, 3H, -CH_3); LCMS (ESI): 396.52 (M+1).

Ethyl-4-(4-methoxyphenyl)-2-methyl-4*H*-benzo[4,5]-thiazolo[3,2-*a*]pyrimidine-3-carboxylate (4d): Yellow solid; m.p.: 122-124 °C; IR (KBr, ν_{max}, cm^{-1}): 1691, 1590, 1465, 1250, 745; ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.67 (dd, *J* = 8, 1.2 Hz, 1H, ArH), 7.56 (d, *J* = 7.6 Hz, 2H, ArH), 7.38 (dd, *J* = 7.6, 1.2 Hz, 1H, ArH), 7.31 (m, 1H, ArH), 7.15 (d, *J* = 7.6 Hz, 2H, ArH), 7.2 (m, 1H, ArH), 6.44 (s, 1H, -CH-), 4.10 (q, *J* = 7.2 Hz, 2H, -CH_2-), 2.28 (s, 3H, -CH_3), 3.72 (s, 3H, -CH_3) 1.20 (t, *J* = 7.2 Hz, 3H, CH_3); LCMS (ESI): 381.45 (M+1).

Ethyl-2-methyl-4-(3,4,5-trimethoxyphenyl)-4*H*-benzo-[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (4e): Yellow solid; m.p.: 168-170 °C; IR (KBr, ν_{max}, cm^{-1}): 3098, 2982, 1690, 1581, 1495, 1272, 1238, 1201, 1077, 835, 739; ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.60 (dd, *J* = 7.8, 1.2 Hz, 1H, ArH), 7.44 (dd, *J* = 7.8, 1.2 Hz, 1H, ArH), 7.28 (m, 1H, ArH), 7.14 (m, 1H, ArH), 6.43 (s, 2H, ArH), 6.30 (s, 1H, -CH-), 4.03 (q, *J* = 6.8 Hz, 2H, -CH_2-), 3.73 (s, 6H, -CH_3), 3.70 (s, 3H, -CH_3), 2.35 (s, 3H, -CH_3), 1.18 (t, *J* = 6.8 Hz, 3H, -CH_3); LCMS (ESI): 441.61 (M+1).

Ethyl-4-(2,5-dimethoxyphenyl)-2-methyl-4*H*-benzo-[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (4f): Yellow solid; m.p.: 162-164 °C; IR (KBr, ν_{max}, cm^{-1}): 3096, 2980, 1694, 1583, 1497, 1271, 1239, 1203, 1075, 836, 739; ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.62 (dd, *J* = 7.8, 1.2 Hz, 1H, ArH), 7.45 (dd, *J* = 6.8, 1.2 Hz, 1H, ArH), 7.30 (m, 1H, ArH), 7.15 (m, 1H, ArH), 6.68 (s, 1H, ArH), 6.43-6.46 (m, 2H, ArH), 6.33 (s, 1H, -CH-), 4.05 (q, *J* = 6.6 Hz, 2H, -CH_2-), 3.90 (s, 3H, -CH_3), 3.68 (s, 3H, -CH_3), 2.37 (s, 3H, -CH_3), 1.20 (t, *J* = 6.6 Hz, 3H, -CH_3); LCMS (ESI): 411.50 (M+1).

Ethyl-7-methyl-5-phenyl-5*H*-thiazolo[3,2-*a*]pyrimi-dine-6-carboxylate (5a): Yellow solid; m.p.: 239-240 °C. IR (KBr, ν_{max}, cm^{-1}): 3095, 2985, 1690, 1542, 1290; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (m, 3H, ArH), 7.33 (m, 2H, ArH), 7.15 (d, *J* = 4.0 Hz, 1H, ArH), 7.02 (d, *J* = 4.0 Hz, 1H, ArH), 6.36 (s, 1H, -CH-), 4.09 (q, *J* = 7.2 Hz, 2H, -CH_2-), 2.67 (s, 3H, -CH_3), 1.20 (t, *J* = 7.2 Hz, 3H, -CH_3); LCMS: 301.22 (M+1).

Ethyl-5-(4-chlorophenyl)-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (5b): Light yellow solid; m.p.: 138-140 °C; IR (KBr, ν_{max}, cm^{-1}): 3070, 2981, 1692, 1570, 1320. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 8.0 Hz, 2H, ArH), 7.26 (d, *J* = 8.0 Hz, 2H, ArH), 6.50 (d, *J* = 4.8 Hz, 1H, ArH), 6.30 (d, *J* = 4.8 Hz, 1H, ArH), 6.17 (s, 1H, CH), 4.05 (q, 2H, -CH_2-), 2,42 (s, 3H, -CH_3), 1.19 (t, *J* = 7.2 Hz, 3H, -CH_3); LCMS: 335.90 (M+1).

Ethyl-5-(4-methoxyphenyl)-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (5d): Yellow solid, m.p.: 133-135 °C; IR (KBr, ν_{max}, cm^{-1}): 3110, 2984, 1687, 1572, 1312; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.4 Hz, 2H, ArH), 6.82 (d, *J* = 8.4 Hz, 2H, ArH), 6.58 (d, *J* = 4.8 Hz, 1H, ArH), 6.25 (d, *J* = 4.8 Hz, 1H, ArH), 6.12 (s, 1H, -CH-), 4.04–4.09 (m, 2H, -CH_2-), 3.75 (s, 3H, -OCH_3), 2.43 (s, 3H, -CH_3), 1,18 (t, *J* = 7.2 Hz, 3H, -CH_3); LCMS: 331.56 (M+1).

Ethyl-7-methyl-5-(3,4,5-trimethoxyphenyl)-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (5e): Yellow solid, m.p.: 152-154 °C; IR (KBr, ν_{max}, cm^{-1}): 3105, 2990, 1691, 1575, 1310; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 4.8 Hz, 1H, ArH), 6.82 (d, *J* = 4.8 Hz, 1H, ArH), 6.49 (s, 2H, ArH), 6.08 (s, 1H, -CH-), 4.06 (q, *J* = 7.0 Hz, 2H, -CH_2), 3.77 (s, 3H, -OCH_3), 3.78 (s, 6H, -OCH_3), 2.44 (s, 3H, -CH_3), 1.16 (t, *J* = 7.0 Hz, 3H, -CH_3); LCMS: 391.35 (M+1).

Ethyl-7-methyl-5-(3,4,5-trimethoxyphenyl)-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (5f): Yellow solid, m.p.: 145-147 °C; IR (KBr, ν_{max}, cm^{-1}): 3101, 2989, 1690, 1578, 1300; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 4.8 Hz, 1H, ArH), 7.02 (s, 2H, ArH), 6.77 (d, *J* = 4.8 Hz, 1H, ArH), 6.89 (s, 1H, ArH), 6.08 (s, 1H, -CH-), 4.05 (q, *J* = 7.2 Hz, 2H, -CH_2), 3.70 (s, 3H, -OCH_3), 3.71 (s, 3H, -OCH_3), 2.48 (s, 3H, -CH_3), 1.18 (t, *J* = 7.2 Hz, 3H, -CH_3); LCMS: 361.53 (M+1).

RESULTS AND DISCUSSION

In an initial endeavour our aim was directed towards the one pot, multi-component reaction of benzaldehyde (**1**), ethyl acetoacetate (**2**) and 2-amino benzthiazole (**3a**) under solvent-free condition using different catalysts under microwaves irradiation to afford pyrimidobenzothiazoles (**4a**) and the results obtained are illustrated in Table-1.

TABLE-1
OPTIMIZATION OF CATALYSTS AND CATALYST LOADING

Catalyst[a]	Catalyst loading (mol %)	Time (min)	Isolated yield (%)
–	–	15	No reaction
$Bi(OTf)_3$	10	15	55
L-Proline	10	15	20
$FeCl_3$	10	15	30
Acetic acid	10	15	Trace
STA	10	15	96
STA	5	15	96
STA	2	15	92

[a]Reaction condition: Ethyl acetoacetate (1.0 mmol), benzaldehyde (1.0 mmol) and 2-aminobenzimidazole (1.0 mmol) under MW irradiation at 300 W.

The results revealed that no product formation in the absence of catalyst after 15 min of irradiation. On the other hand, the use of catalysts such as bismuth triflate, $FeCl_3$, L-proline and acetic acid furnished the products to little extent. Use of bismuth triflate afforded 55% yield, L-proline afforded 20% yield, $FeCl_3$ furnished 30% yield and acetic acid gave trace quantity of the yield of product. However, it was found that the use of silicotungstic acid (STA) as a catalyst afforded excellent yield of the product compared to the bismuth triflate, $FeCl_3$, L-proline and acetic acid under microwave irradiation and solvent-free condition. Further, we assessed the effect of catalyst loading on the reaction conversion and it was observed that 5 mol% catalyst is enough to drive the reaction towards completion (95% yield). The use of 2 mol% of STA decreased the conversion of product slightly (92%).

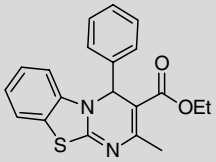
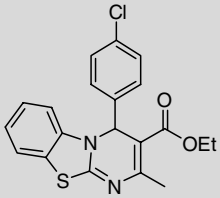
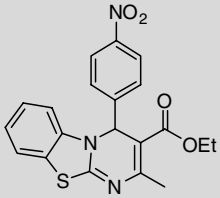
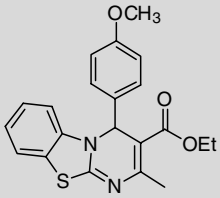
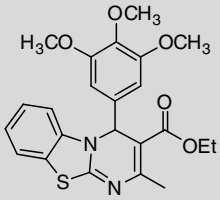
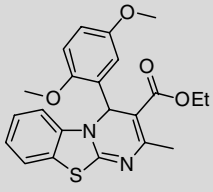
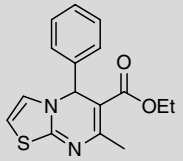
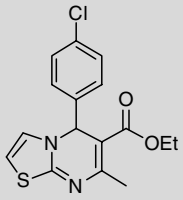
To study the generality of this protocol, we extended the optimized protocol for the synthesis of pyrimidothiazoles (**5a-f**) by replacing 2-amino benzthiazole with 2-amino thiazole. This reaction also provided the excellent yield of product *i.e.* pyrimidothiazoles (92%) under identical reaction conditions.

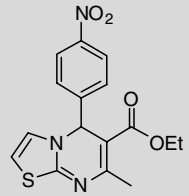
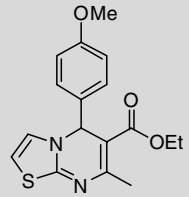
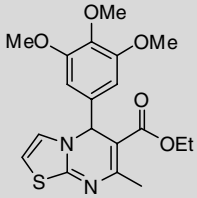
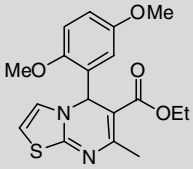
To study the scope for substrate, we further extended our work with different aromatic aldehydes to prepare a series of

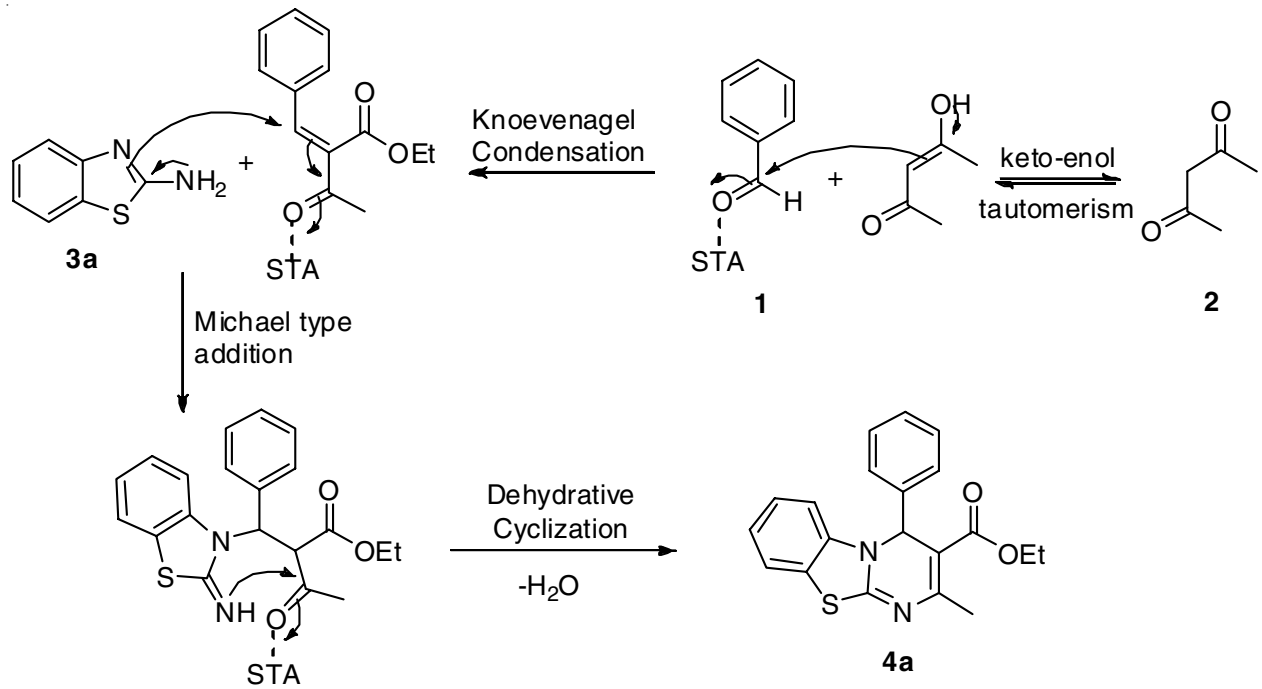
pyrimidothiazoles (**4a-f**) and pyrimidobenzothiazoles (**5a-f**) and the results are presented in Table-2. All the aromatic aldehydes furnished the desired products in good to excellent yields. All the synthesized compounds were characterized by using IR and ^{1}H NMR and mass spectral data.

The probable mechanism for the formation of product is illustrated in **Scheme-II**. The Knoevenagel condensation of ethyl acetoacetate (**2**) and benzaldehyde (**1**) leads to the formation of Knoevenagel adduct which on Michael type addition followed by the dehydrative cyclization afforded the desired product **4a**.

TABLE-2
STA CATALYZED MULTI-COMPONENT SYNTHESIS OF PYRIMIDOTHIAZOLES AND PYRIMIDOBENZOTHIAZOLES UNDER MW IRRADIATION

Compound	Structure	Time (min)	Colour	Isolated yield (%)	m.p. (°C)
4a		15	Yellow	95	176-178 (178-180) [22]
4b		15	Yellow	92	88-90 (86-88) [23]
4c		20	Brown	90	169-171 (170-172) [23]
4d		20	Yellow	91	122-124
4e		20	Yellow	90	168-170
4f		20	Yellow	88	162-164
5a		20	Brown	92	239-240 (240-241) [23]
5b		25	Yellow	94	138-140 (138-139) [24]

5c		25	Brown	86	135-137 (137-138) [24]
5d		20	Black	92	133-135 (135-136) [24]
5e		20	Yellow	90	152-154
5f		25	Yellow	85	145-147



Scheme-II: Probable mechanism for the formation of pyrimidobenzothiazoles

Conclusion

In conclusion, we have developed a simple heteropolyacid (silicotungstic acid) catalyzed, one-pot, multi-component protocol for the synthesis of pyrimidothiazoles and pyrimidobenzothiazoles *via* condensation of ethyl acetoacetate, benzaldehyde and 2-amino thiazole or 2-amino benzthiazole under solvent-free condition using microwave irradiation. The advantages of this method are solvent-free conditions, short reaction time, easy purification, high yield and economic availability of the catalyst.

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