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ORIGINAL ARTICLE

A facile, solvent and catalyst free, microwave assisted one pot synthesis of hydrazinyl thiazole derivatives



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Abstract A rapid synthesis of hydrazinyl thiazoles under solvent and catalyst free condition is reported within 30 s. A series of aryl ketones/4-benzoyl pyridine thiosemicarbazone, thiosemicarbazide and α -haloketones were used. This is an environmentally benign microwave assisted and efficient method for rapid synthesis of hydrazinyl thiazoles.

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1. Introduction

In the recent years thiazoles and their derivatives have attracted medicinal chemists because of their biological properties and their application found in drug development for the treatment of allergies [1], hypertension [2], inflammation [3], schizophrenia [4], antibacterial [5], HIV infections [6], hypnotics [7], and more recently for treatment of pain [8], as fibrinogen receptor antagonist with antithrombotic activity [9], and as new inhibitors of bacterial DNA gyrase B. [10]. In the proposed investigation the compounds to be synthesized contain a thiazole moiety in the total heterocyclic system. There are many examples of biologically active thiazoles

which showed very interesting pharmacological properties such as anti-inflammatory, anti-hypertensive, antibacterial and anti HIV infectious etc. Amino thiazoles are known to be ligands of estrogen receptors [11], as well as novel class of adenosine receptor antagonists [12], moreover organic compounds containing thiazole nucleus are found to possess high second order hyper polarizability [13–16]. In view of the importance of thiazoles and their derivatives several methods for the synthesis of thiazole derivatives were developed [17,18]. However in spite of their potential utility many of these reported methods suffer from drawbacks such as harsh reaction conditions, wastage of solvents and catalyst which have to be recovered, treated and disposed. Microwave assisted organic reactions using dry media have attracted much interest because of the simplicity in operation, greater selectivity and rapid synthesis of a variety of heterocyclic compounds. Thus it was thought worthwhile to synthesize the thiazole derivatives using green route that is the microwave organic reaction enhancement method (MORE). In this context the present investigation leads to the microwave assisted one pot synthesis of not yet synthesized newer heterocyclic moiety with thiazole nucleus.

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2. Experimental

2.1. Instruments

The IR spectrum was recorded in an AVATAR-330 FT-IR spectrophotometer and only noteworthy absorption levels (reciprocal centimeters) were listed. ^1H NMR spectra were recorded at 400 and 500 MHz on a Bruker AMX 400 and 500 MHz spectrophotometer using CDCl_3 or $\text{DMSO-}d_6$ as solvent and TMS as the internal standard. ^{13}C NMR spectra were recorded at 100 and 125 MHz on a Bruker AMX 400 and 500 MHz spectrophotometer using CDCl_3 or $\text{DMSO-}d_6$ as the solvent. HRMS (ESI) was carried out in a Bruker Maxis instrument in the School of Chemistry, University of Hyderabad. Elemental analyses (CHN) were recorded on a Thermo Finnigan Flash EA 1112 analyzer at the School of Chemistry, University of Hyderabad. Routine monitoring of the reactions was performed by TLC, using silica gel plates (Merck 60 F254) and compounds were visualized with a UV light at 254 nm.

3. Synthesis

3.1. General procedure for the synthesis of thiazoles (4a–i, 6a–j)

Equimolar amounts of aryl ketones (2.0 mmol), thiosemicarbazide (2.0 mmol) and substituted phenacyl bromide (2.0 mmol) are mixed and subjected to microwave irradiation for 30–175 s at a heating of 300 W. After the reaction is completed it is taken out, the solid product is recrystallized from ethanol to get pure compounds (4–i, 6a–j).

3.1.1. (Z)-4-(4-methoxyphenyl)-2-(2-(1-phenylethylidene)hydrazinyl)thiazole (4a)

White solid; mp 230–233 °C; ^1H NMR (400 MHz, CDCl_3) 2.58 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.88 (s, CH, thiazole), 7.45 (s, 3H), 7.69–7.71 (d, 4H), 7.80 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) 15.24, 102.47, 126.52, 126.52, 126.94, 127.49, 128.63, 128.59, 130.33, 135.74, 136.34, 141.74, 154.21, 169.91; FT-IR (KBr) 1509.96, 1616.91, 3121.68; HRMS (ESI-MS) Exert M. W: 323.1092; found 324.1173 ($\text{M} + \text{H}^+$); CHN analysis: $\text{C}_{18}\text{H}_{17}\text{N}_3\text{OS}$. Anal. Calcd. (%) for: C, 66.85; H, 5.30; N, 12.99; found (%): C, 66.72; H, 5.36; N, 12.85.

3.1.2. (Z)-4-(4-methoxyphenyl)-2-(2-(1-(4-nitrophenyl)ethylidene)hydrazinyl)thiazole (4b)

Orange yellow solid; mp 191–194 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.59 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.69 (s, CH, thiazole), 6.99, 7.02 (d, 2H), 7.67, 7.69 (d, 2H), 7.95, 7.98 (d, 2H) 8.28, 8.30 (d, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 15.74, 55.53, 99.59, 115.02, 123.91, 127.27, 127.45, 139.64, 142.18, 153.43, 161.28, 169.94; FT-IR (KBr) 1585.90, 1613.00, 3198.89; HRMS (ESI-MS) Exert M. W: 368.0943; found: 369.1022 ($\text{M} + \text{H}^+$); CHN analysis: $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_3\text{S}$. Anal. Calcd. (%) for: C, 58.68; H, 4.38; N, 15.21; found (%): C, 58.45; H, 4.31; N, 15.12.

3.1.3. (Z)-4-(4-methoxyphenyl)-2-(2-(1-(4-methoxyphenyl)ethylidene)hydrazinyl)thiazole (4c)

Dirty white solid; mp 270–273 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.38 (s, 3H, CH_3), 3.82 (s, 6H, OCH_3), 6.63 (s,

CH, thiazole), 6.91–6.96 (t, 4H), 7.66, 7.68 (d, 2H), 7.73, 7.75 (d, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.68, 55.43, 100.02, 113.95, 114.58, 123.13, 127.19, 127.60, 128.93, 129.30, 144.76, 151.90, 160.43, 161.17, 169.60; FT-IR (KBr) 1576.23 1621.31, 3143.13; HRMS (ESI-MS) Exert M. W: 353.1198; found: 354.1277 ($\text{M} + \text{H}^+$); CHN analysis: $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$. Anal. Calcd. (%) for: C, 64.57; H, 5.42; N, 11.89; found (%): C, 64.63; H, 5.77; N, 11.56.

3.1.4. (Z)-4-(4-chlorophenyl)-2-(2-(1-(4-methoxyphenyl)ethylidene)hydrazinyl)thiazole (4d)

Dirtywhite solid; mp 185–188 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.52(s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.61 (s, CH, thiazole), 6.99–7.01(d, 2H), 7.44–7.45 (d, 2H), 7.66–7.68 (d, 2H), 7.79–7.81 (d, 2H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 16.04, 55.51, 98.92, 115.02, 119.97, 126.72, 127.21, 128.71, 130.66, 136.12, 140.85, 156.18, 161.24, 169.86; FT-IR (KBr)1567.12, 1613.57, 3336.99; HRMS (ESI-MS) Exert M. W: 357.0703; found: 358.0782 ($\text{M} + \text{H}^+$); CHN analysis: $\text{C}_{18}\text{H}_{16}\text{ClN}_3\text{OS}$. Anal. Calcd. (%) for: C, 60.41; H, 4.51; N, 11.74; found (%): C, 60.76; H, 4.35; N, 11.81.

3.1.5. (Z)-4-(1-(2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazono)ethyl)phenol (4e)

White solid; mp 174–177 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 1.90 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.62 (s, CH, thiazole), 6.64–6.67(d, 2H), 6.78–6.80 (d, 2H), 6.88–6.90 (d, 3H), 7.27–7.28 (d, H), 7.57–7.58 (d, H), 8.75 (s, OH); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 15.42, 55.39, 99.16, 114.80, 115.68, 127.09, 128.26, 159.90, 160.95, 169.26; FT-IR (KBr) 1587.25, 1615.66, 3367.45; HRMS (ESI-MS) Exert M. W: 339.1041; found: 340.1122 ($\text{M} + \text{H}^+$); CHN analysis: $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$. Anal. Calcd. (%) for: C, 63.70; H, 5.05; N, 12.38; found (%): C, 63.66; H, 5.36; N, 12.75.

3.1.6. (Z)-4-(4-chlorophenyl)-2-(2-(1-(4-chlorophenyl)ethylidene)hydrazinyl)thiazole (4f)

Pale white solid; mp 197–200 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.52(s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.36 (s, CH, thiazole), 7.45–7.48 (d, H), 7.52–7.53 (d, H), 7.57–7.58 (d, H), 7.72 (S, H) 7.76–7.77 (d, H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 14.34, 105.44, 127.71, 127.85, 127.97, 128.90, 128.98, 129.09, 129.24, 129.79, 130.53, 133.92, 170.26; FT-IR (KBr) 1587.34, 1616.79, 3439.05; HRMS (ESI-MS) Exert M. W: 361.0207; found: 362.0287 ($\text{M} + \text{H}^+$); CHN analysis: $\text{C}_{17}\text{H}_{13}\text{Cl}_2\text{N}_3\text{S}$. Anal. Calcd. (%) for: C, 56.36; H, 3.62; N, 11.60; found (%): C, 56.37; H, 3.57; N, 11.54.

3.1.7. (Z)-4-(4-chlorophenyl)-2-(2-(1-(3,4-dimethoxyphenyl)ethylidene)hydrazinyl)thiazole (4g)

Dirtywhite solid; mp 195–198 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.27 (s, 3H, CH_3), 3.79, 3.80 (s, 6H, OCH_3), 6.96 (s, CH, thiazole), 6.95–6.98 (d, H), 7.27–7.28 (d, 2H), 7.41–7.42 (d, H), 7.44–7.45 (d, H) 7.46–7.47 (d, H), 7.86–7.87 (d, 2H), 7.87–7.89 (d, H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 14.13, 55.95, 105.17, 109.19, 111.31, 119.45, 123.63, 127.71, 129.09, 130.97, 132.39, 133.97, 147.36, 148.98, 149.56, 150.25, 170.60; FT-IR (KBr) 1586.57, 1626.69, 3431.21 ;HRMS (ESI-MS) Exert M. W: 387.0808; found: 388.0884 ($\text{M} + \text{H}^+$); CHN analysis $\text{C}_{19}\text{H}_{18}\text{ClN}_3\text{O}_2\text{S}$. Anal. Calcd. (%) for: C, 58.83; H, 4.68; N, 10.83; found (%): C, 58.53; H, 4.57; N, 10.73.

3.1.8. (Z)-4-(4-methoxyphenyl)-2-(2-(1-(thiophen-2-yl) ethylidene) hydrazinyl) thiazole (**4h**)

Pale yellow solid; mp 230–233 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.60 (s, 3H, CH₃), 3.86 (s, 3H, OCH₃), 6.63 (s, CH, thiazole), 7.01, 7.03 (d, 2H), 7.44–7.48 (m, 4H), 7.70, 7.82 (dd, H); ¹³C NMR (100 MHz, CDCl₃) δ 16.00, 55.47, 98.86, 115.01, 120.02, 126.70, 127.20, 128.67, 130.61, 136.15, 140.93, 156.17, 161.25, 169.90; FT-IR (KBr) 1583.56, 1616.44, 3134.25; HRMS (ESI-MS) Exert M. W: 329.0657; found: 330.0732 (M+H⁺); CHN analysis: C₁₆H₁₅N₃O₂S. Anal. Calcd. (%) for: C, 58.33; H, 4.59; N, 12.76; found (%): C, 58.47; H, 4.51; N, 12.86.

3.1.9. (E)-2-(2-(1-(furan-2-yl)ethylidene)hydrazinyl)-4-(4-methoxyphenyl)thiazole (**4i**)

Yellow solid; mp 172–175 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.49 (s, 3H, CH₃), 3.85 (s, 3H, OCH₃), 6.62 (s, CH, thiazole), 6.53 (s, H) 6.89, 6.90 (d, 2H), 7.56 (s, 2H) 7.65, 7.67 (d, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 15.13, 55.49, 98.91, 112.21, 112.92, 114.99, 120.03, 127.18, 140.84, 145.11, 147.36, 150.37, 161.21, 169.35; FT-IR (KBr) 1505.32, 1617.36, 3139.73; HRMS (ESI-MS) Exert M. W: 313.0885; found: 314.0966 (M+H⁺); CHN analysis: C₁₆H₁₅N₃O₂S. Anal. Calcd. (%) for: C, 61.32; H, 4.82; N, 13.41; found (%): C, 61.82; H, 4.22; N, 13.75.

3.1.10. (Z)-2-(2-(4-chlorophenyl)(phenyl)methylene)hydrazinyl)-4-(4-methoxyphenyl)thiazole (**6a**)

Yellow solid; mp 71–73 °C; ¹H NMR (400 MHz, CDCl₃) δ 3.82 (s, 3H, OCH₃), 6.74 (s, CH, thiazole), 6.87, 6.89 (d, 2H), 7.24–7.26 (t, 3H), 7.50–7.52 (d, 2H) 7.54–7.57 (q, 4H), 7.63, 7.65 (d, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 55.34, 102.04, 114.00, 127.08, 127.18, 128.47, 128.61, 129.42, 130.03, 130.14, 130.25, 130.36, 136.01, 136.72, 159.38, 168.27; FT-IR (KBr) 1607.38, 1650.78, 3376.22; HRMS (ESI-MS) Exert M. W: 419.0859; found: 420.0933 (M+H⁺); CHN analysis: C₂₃H₁₈ClN₃O₂S. Anal. Calcd. (%) for: C, 65.78; H, 4.32; N, 10.01; found (%): C, 65.66; H, 4.57; N, 9.81.

3.1.11. (Z)-4-(4-chlorophenyl)-2-(2-(4-chlorophenyl)(phenyl)methylene)hydrazinyl)thiazole (**6b**)

White solid; mp 165–178 °C; ¹H NMR (400 MHz, CDCl₃) δ 6.87 (s, CH, thiazole), 7.38–7.40 (q, 7H), 7.71–7.74 (q, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 104.44, 113.76, 128.61, 128.42, 127.34, 127.19, 128.11, 129.62, 131.33, 132.47, 132.25, 133.76, 136.91, 137.87, 159.38 169.87; FT-IR (KBr) 1553.95, 1605.37, 3438.63; HRMS (ESI-MS) Exert M. W: 423.0364; found: 424.0445 (M+H⁺); CHN analysis: C₂₂H₁₅Cl₂N₃S. Anal. Calcd. (%) for: C, 62.27; H, 3.56; N, 9.90; found (%): C, 62.37; H, 3.53; N, 9.95.

3.1.12. (Z)-2-(2-(4-chlorophenyl)(phenyl)methylene)hydrazinyl)-4-(4-nitrophenyl)thiazole (**6c**)

Yellow solid; mp 187–190 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.12 (s, CH, thiazole), 7.25 (s, H), 7.37 (s, H), 7.83–7.87 (t, 3H), 8.32, 8.34 (d, 2H), 8.39, 8.40 (d, 2H) 8.41, 8.42 (d, 2H), 8.66 (s, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 103.54, 116.77, 121.97, 126.19, 131.23, 133.63, 135.22, 148.68, 149.63, 165.03; FT-IR (KBr) 1561.64, 1616.44, 1638.36, 3112.33; HRMS (ESI-MS) Exert M. W: 434.0604; found: 435.0662 (M+H⁺); CHN analysis: C₂₂H₁₅ClN₄O₂. Anal. Calcd. (%) for: C, 60.76; H, 3.48; N, 12.88; found (%): C, 60.85; H, 3.41; N, 12.76.

3.1.13. (Z)-2-(2-(4-fluorophenyl)(phenyl)methylene)hydrazinyl)-4-(4-methoxyphenyl)thiazole (**6d**)

White solid; mp 165–167 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.88 (s, 3H, OCH₃), 7.03 (s, CH, thiazole), 7.06, 7.07 (d, 2H), 7.08–7.09 (t, H), 7.61–7.62 (t, 2H) 7.59–7.60 (d, 2H), 7.91, 7.93 (t, H), 7.90, 7.91 (d, H), 7.86, 7.87 (d, 2H), 7.85, 7.85 (d, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 55.97, 114.90, 129.25, 129.56, 132.34, 136.68, 150.47, 162.31, 164.81, 165.01; FT-IR (KBr) 1610.96, 1638.36, 3002.74; HRMS (ESI-MS) Exert M. W: 403.1155; found: 404.1234 (M+H⁺); CHN analysis: C₂₃H₁₈FN₃O₂S. Anal. Calcd. (%) for: C, 68.47; H, 4.50; N, 10.41; found (%): C, 68.37; H, 4.43; N, 10.56.

3.1.14. (Z)-4-(4-chlorophenyl)-2-(2-(4-fluorophenyl)(phenyl)methylene)hydrazinyl)thiazole (**6e**)

Dirty white solid; mp 171–173 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.13 (s, CH, thiazole), 7.06, 7.07 (d, 2H), 7.08–7.09 (t, H), 7.61–7.62 (t, H) 7.59–7.60 (d, 2H), 7.91, 7.93 (t, H), 7.90, 7.91 (d, 2H), 7.86, 7.87 (d, 2H), 7.85, 7.85 (d, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 105.56, 113.85, 128.65, 129.33, 132.44, 135.78, 151.67, 163.61, 164.11, 166.43; FT-IR (KBr) 1531.51, 1619.48, 3368.65; HRMS (ESI-MS) Exert M. W: 407.0659; found: 408.0730 (M+H⁺); CHN analysis: C₂₂H₁₅ClFN₃S. Anal. Calcd. (%) for: C, 64.78; H, 3.71; N, 10.30; found (%): C, 64.78; H, 3.71; N, 10.30.

3.1.15. (Z)-4-(2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazono)(phenyl)methyl)aniline (**6f**)

Pale yellow solid; mp 120–123 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.85 (s, 3H, OCH₃), 7.12 (s, CH, thiazole), 7.25 (s, H) 7.37 (s, H), 7.83–7.87 (t, 4H), 8.32, 8.34 (d, 2H), 8.39, 8.40 (d, 2H) 8.41, 8.42 (d, 3H), 8.66 (s, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 56.44, 104.64, 117.63, 129.79, 131.98, 132.22, 132.73, 133.18, 133.44, 133.25, 133.95, 134.56, 136.40, 142.08, 153.99, 169.94; FT-IR (KBr) 1605.64, 1624.66, 3379.00; HRMS (ESI-MS) Exert M. W: 400.1358; found: 401.1436 (M+H⁺); CHN analysis: C₂₃H₂₀ON₄S. Anal. Calcd. (%) for: C, 65.26; H, 4.23; N, 13.84; found (%): C, 65.73; H, 4.33; N, 13.92.

3.1.16. (Z)-2-(2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazono)(phenyl)methyl)-5-nitroaniline (**6g**)

Yellow solid; mp 130–133 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.64 (s, 2H, NH₂), 3.91 (s, 3H, OCH₃), 7.15 (s, CH, thiazole), 7.28 (s, H) 7.39–7.41 (t, 2H), 7.46–7.49 (q, 3H), 7.55–7.63 (q, 2H) 7.78–7.80 (d, 2H), 7.88–7.95 (q, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 56.17, 106.23, 113.95, 126.74, 127.96, 128.14, 128.27, 128.61, 131.40, 132.34, 135.72, 149.49, 152.09, 161.52, 166.76; FT-IR (KBr) 1531.51, 1614.31, 3363.47; HRMS (ESI-MS) Exert M. W: 445.1209; found: 446.1256 (M+H⁺); CHN analysis: C₂₃H₁₉N₅O₃S. Anal. Calcd. (%) for: C, 62.01; H, 4.30; N, 15.72; found (%): C, 58.86; H, 3.51; N, 15.45.

3.1.17. (Z)-2-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazono)(phenyl)methyl)-5-nitroaniline (**6h**)

Dirty white solid; mp 150–153 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.64 (s, 2H, NH₂), 7.56 (s, CH, thiazole), 7.28 (s, 2H) 7.39–7.41 (t, 2H), 7.46–7.49 (q, 2H), 7.55–7.63 (q, 2H) 7.78–7.80 (d, 2H), 7.88–7.95 (q, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 104.74, 115.55, 126.74, 127.96,

128.14, 128.27, 128.61, 131.40, 135.72, 149.49, 152.09, 166.98; FT-IR (KBr) 1589.04, 1616.44, 1632.88, 3134.25; HRMS (ESI-MS) Exert M. W: 449.0713; found: 450.0166 ($M+H^+$); CHN analysis: $C_{22}H_{16}ClN_5O_2S$. Anal. Calcd. (%) for: C, 58.73; H, 3.58; N, 15.57; found (%): C, 58.77; H, 3.63; N, 15.81.

3.1.18. (*Z*)-4-chloro-2-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazono)(phenyl)methyl)aniline (**6i**)

Yellow solid; mp 165–168 °C; 1H NMR (400 MHz, DMSO- d_6) δ 3.51 (s, 2H, NH_2), 7.40 (s, CH, thiazole), 7.28 (s, H) 7.39–7.41 (t, 2H), 7.46–7.49 (q, 2H), 7.55–7.63 (q, 2H) 7.78–7.80 (d, 2H), 7.88–7.95 (q, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 104.73, 116.11, 127.53, 127.93, 128.47, 128.61, 129.42, 130.03, 130.14, 131.40, 135.72, 149.49, 152.09, 166.98; FT-IR (KBr) 1594.52, 1627.40, 3139.73; HRMS (ESI-MS) Exert M. W: 438.0473; found: 439.0550 ($M+H^+$); CHN analysis: $C_{22}H_{16}Cl_2N_4S$. Anal. Calcd. (%) for: C, 60.14; H, 3.67; N, 12.75; found (%): C, 60.25; H, 3.61; N, 12.86.

3.1.19. 4-(4-chlorophenyl)-2-(2-(dip-tolylmethylene)hydrazinyl)thiazole (**6j**)

Pale white solid; mp 190–193 °C; 1H NMR (400 MHz, DMSO- d_6) δ 2.63 (s, 6H, CH_3), 6.74 (s, CH, thiazole), 6.87, 6.89 (d, 2H), 7.24–7.26 (t, 3H), 7.50–7.52 (d, 2H) 7.54–7.57 (q, 3H), 7.63, 7.65 (d, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 13.73, 104.44, 113.22, 126.56, 127.44, 128.69, 128.76, 129.42, 131.83, 131.91, 132.54, 136.11, 137.63, 159.58, 167.22; FT-IR (KBr) 1557.38, 1629.83, 3135.77; HRMS (ESI-MS) Exert MW: 417.1066; found: 418.1144 ($M+H^+$); CHN analysis: $C_{24}H_{20}ClN_3S$. Anal. Calcd. (%) for: C, 68.97; H, 4.82; N, 10.05; found (%): C, 68.63; H, 4.73; N, 10.11.

3.2. General procedure for the synthesis of thiazoles (**8a–d**)

Equimolar quantities of 4-benzoyl pyridine thiosemicarbazone (2.0 mmol) and substituted phenacyl bromide (2.0 mmol) **8a–d** are mixed and must be subjected to microwave irradiation for 50–120 s at a heating of 400 W. After the completion of reaction it is taken out and cooled to room temperature. The solid crude product was washed with acetonitrile (CH_3CN) solvent to get pure compounds **8a–d**.

3.2.1. (*Z*)-4-phenyl-2-(2-(phenyl(pyridin-4-yl)methylene)hydrazinyl)thiazole (**8a**)

Orange solid; mp 205–207 °C; 1H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, CH, thiazole), 7.06 (s, H), 7.35–7.39 (q, 4H), 7.46, 7.48 (d, 2H) 7.61–7.67 (q, 3H), 7.71, 7.73 (d, 2H) 8.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.47, 125.92, 125.96, 128.40, 128.78, 129.48, 130.37, 130.62, 131.10, 159.13, 166.22; FT-IR

(KBr)1605.48, 1632.52, 3443.94; HRMS (ESI-MS) Exert M. W: 356.1096; found: 357.1176 ($M+H^+$); CHN analysis: $C_{21}H_{16}N_4S$. Anal. Calcd. (%) for: C, 70.76; H, 4.52; N, 15.72; found (%): C, 70.41; H, 4.62; N, 15.83.

3.2.2. (*Z*)-4-(4-methoxyphenyl)-2-(2-(phenyl(pyridin-4-yl)methylene)hydrazinyl)thiazole (**8b**)

Orange solid; mp 175–178 °C; 1H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H, OCH_3), 6.89 (s, CH, thiazole), 6.89–6.91 (d, 2H), 7.31, 7.32 (d, 2H), 7.33, 7.34 (d, 2H) 7.59 (s, H), 7.61 (s, H), 7.62–7.63 (d, 2H) 7.64–7.65 (d, H) 7.66, 7.67 (d, H) 8.61 (broad singlet, H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.35, 103.00, 114.09, 121.36, 127.19, 127.27, 128.61, 129.86, 130.45, 130.75, 146.66, 147.21, 151.50, 159.56, 166.95; FT-IR (KBr) 1602.53, 1633.28, 3298.63; HRMS (ESI-MS) Exert M. W: 386.1201; found: 387.1281 ($M+H^+$); CHN analysis: $C_{22}H_{18}N_4OS$. calcd. for. Anal. Calcd. (%) for: C, 68.37; H, 4.69; N, 14.50; found (%): C, 68.47; H, 4.77; N, 14.61.

3.2.3. (*Z*)-4-(4-chlorophenyl)-2-(2-(phenyl(pyridin-4-yl)methylene)hydrazinyl)thiazole (**8c**)

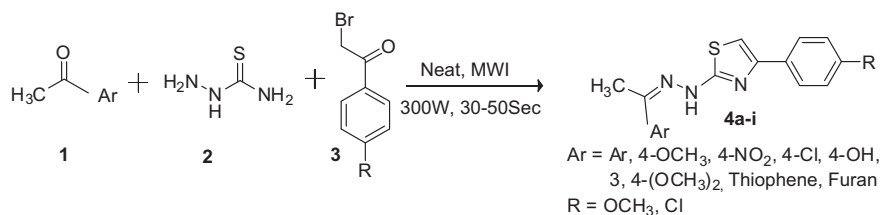
Orange solid; mp 207–209 °C; 1H NMR (400 MHz, DMSO- d_6) δ 6.90 (s, CH, thiazole), 6.99 (s, 2H), 7.35, 7.39 (d, 2H), 7.54 (s, 2H), 7.67, 7.76 (d, 3H) 8.65 (s, 2H), 8.91 (s, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 105.54, 117.79, 123.64, 127.17, 128.68, 128.94, 145.16, 148.22, 149.73, 1597.66, 167.53; FT-IR (KBr) 1599.70, 1635.41, 3295.44; HRMS (ESI-MS) Exert M. W: 390.0706; found: 391.0787 ($M+H^+$); CHN analysis: $C_{21}H_{15}ClN_4S$. Anal. Calcd. (%) for: C, 64.53; H, 3.87; N, 14.33; found (%): C, 64.63; H, 3.71; N, 14.61.

3.2.4. (*Z*)-4-(4-nitrophenyl)-2-(2-(phenyl(pyridin-4-yl)methylene)hydrazinyl)thiazole (**8d**)

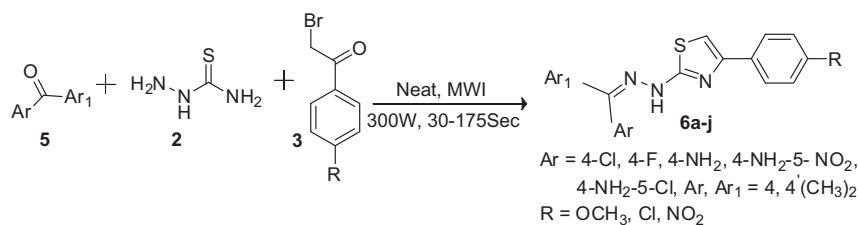
Orange solid; mp 102–105 °C; 1H NMR (400 MHz, DMSO- d_6) δ 7.14 (s, CH, thiazole), 7.17, 7.18 (d, 2H), 7.44–7.48 (t, 3H), 7.58, 7.60 (d, 2H), 7.80, 7.82 (d, 2H) 7.97, 8.04 (d, 2H), 8.54 (s, H) 8.63, 8.64 (d, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 107.68, 120.80, 122.46, 128.28, 128.62, 129.64, 130.56, 131.01, 131.37, 135.83, 142.02, 142.02, 142.79, 148.55, 167.28; FT-IR (KBr) 1556.16, 1605.48, 3243.84; HRMS (ESI-MS) Exert M. W: 401.0946; Found: 402.1025 ($M+H^+$); CHN analysis: $C_{21}H_{15}N_5O_2S$. Anal. Calcd. (%) for: C, 62.83; H, 3.77; N, 17.45; found (%): C, 65.72; H, 3.71; N, 17.56.

4. Results and discussion

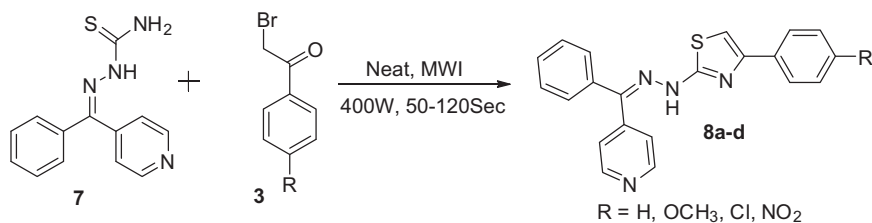
One pot processes are very attractive and sustainable in modern synthetic organic chemistry. A greener and more facile procedure for the synthesis of hydrazinyl thiazoles was developed from readily available aryl ketones/4-benzoylpyridine



Scheme 1 Solvent and catalyst free synthesis of hydrazinyl thiazoles (**4a–i**).



Scheme 2 Solvent and catalyst free synthesis of hydrazinyl thiazoles (**6a-j**).



Scheme 3 Solvent and catalyst free synthesis of hydrazinyl thiazoles (**8a-d**).

Table 1 Microwave-assisted neat synthesis of hydrazinyl thiazoles (**4a-i**, **6a-j**).

Entry	Aryl ketones, R ₁ (1), Ar/Ar ₁ (5)	α -Haloketones R ₂ (3)	Time/s	Yield %
1	Acetophenone	4-Methoxy α -haloketone	40	70
2	4-NO ₂ acetophenone	4-Methoxy α -haloketone	45	70
3	4-OCH ₃ acetophenone	4-Methoxy α -haloketone	45	80
4	4-Cl acetophenone	4-Methoxy α -haloketone	30	75
5	4-OH acetophenone	4-Methoxy α -haloketone	50	60
6	4-Cl acetophenone	4-Chloro α -haloketone	30	70
7	3,4-(OCH ₃) ₂ acetophenone	4-Chloro α -haloketone	30	75
8	2-Acetyl thiophenone	4-Methoxy α -haloketone	45	75
9	2-Acetyl furan	4-Methoxy α -haloketone	30	70
10	4-Cl benzophenone	4-Methoxy α -haloketone	120	75
11	4-Cl benzophenone	4-Chloro α -haloketone	30	70
12	4-Cl benzophenone	4-Nitro α -haloketone	60	75
13	4-F benzophenone	4-Methoxy α -haloketone	55	80
14	4-F benzophenone	4- α -Chlorohaloketone	155	70
15	4-Amino benzophenone	4-Methoxy α -haloketone	55	70
16	2-Amino-5-nitro benzophenone	4-Methoxy α -haloketone	175	80
17	2-Amino-5-nitro benzophenone	4- α -Chlorohaloketone	90	70
18	2-Amino,-5chloro benzophenone	4- α -Chlorohaloketone	90	80
19	4,4'-Dimethylbenzophenone	4- α -Chlorohaloketone	145	80

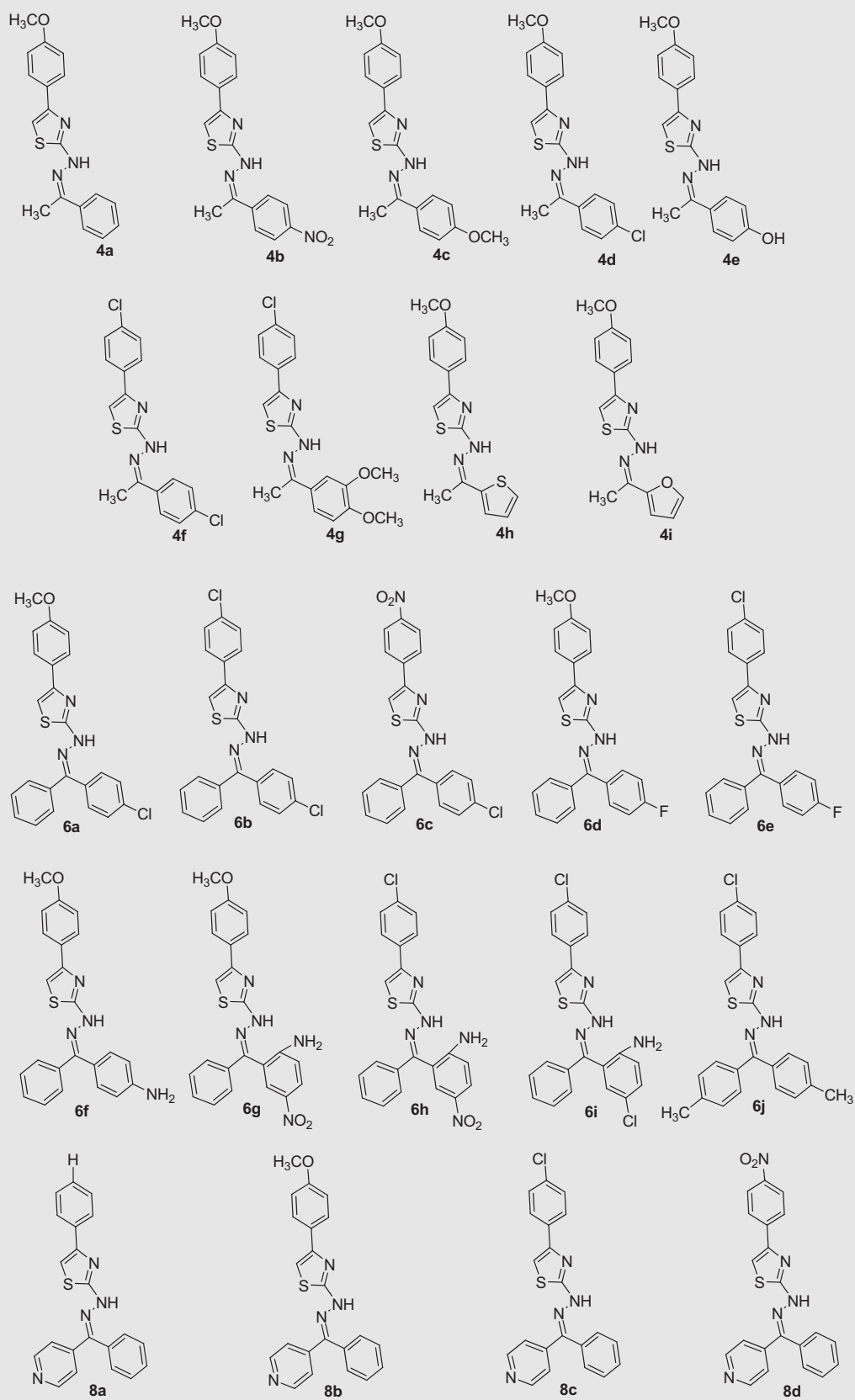
Table 2 Microwave-assisted neat synthesis of hydrazinyl thiazoles (**8a-d**).

Entry	4-Benzoyl pyridinethiosemicarbazone (7)	α -Haloketones R ₂ (3)	Time/s	Yield (%)
1	4-Benzoyl pyridine thiosemicarbazone	α -Haloketone	50	65
2	4-Benzoyl pyridine thiosemicarbazone	4-OCH ₃ α -haloketone	120	85
3	4-Benzoyl pyridine thiosemicarbazone	4-Cl, α -haloketone	50	75
4	4-Benzoyl pyridine thiosemicarbazone	4-NO ₂ α -haloketone	75	80

thiosemicarbazones, thiosemicarbazide and α -haloketones. The eco-friendly attributes of this process are solvent and catalyst free conditions. The reaction protocol includes advantages of short reaction time and easy work-up or purification step and the high purity of product.

Hence we examined the reaction of acetophenones with thiosemicarbazide and α -haloketones under different conditions

using MW activation; we found that the best result was obtained when the reaction mixture was irradiated at a power level of 300 W for 30–175 s and 400 W for 50–120 s. Encouraged by the result, a series of hydrazinyl thiazoles were synthesized (Schemes 1 and 2) using substituted acetophenones/benzophenones under optimized conditions and the results are shown in Table 1. Here we found that the reaction of

Table 3 Structure of hydrazinyl thiazole compounds **4a-i**, **6a-j**, **8a-d**.

acetophenone having the electron donating methoxy group was rapid compared to that one having electron releasing, electron withdrawing groups and also high yield of the product was obtained when there is the electron donating group in the *para* position. However among the electron releasing substituents, the *para*-hydroxy substituted acetophenone is relatively less reactive and requires 50 s, 300 W of microwave irradiation for the completion of the reaction. The yield is also found to be very low when compared to all the synthesized compounds (**4e**).

When the reaction protocol was further extended to 4-Benzoyl pyridine no appreciable conversion took place Scheme 3. Therefore even the reaction time and conditions the increasing temperature. However the hydrazones of 4-benzoyl pyridine react efficiently with α -haloketones affording the products (Table 2).

The results of all the reactions are given in Tables 1 and 2. The structures of all the synthesized compounds (Table 3), the synthesized compound **4b** ^1H NMR (S1), ^{13}C NMR (S2), HSQC (S3) and HRMS (S4), were confirmed, in part, by the presence of C=N signals around 166–170 ppm (indication of thiazole ring) in the ^{13}C NMR spectra. The singlet around 6.69 ppm in the ^1H NMR spectrum of these compounds corresponds to methine proton of the thiazole ring. To give further evidence for the formation of the thiazole ring, HSQC spectrum for compound was recorded. In that spectrum the proton signal at 6.69 ppm is well correlated with the signal at 99.5 ppm. So the signal around 6.69–7.24 ppm in all the cases, is due to methine proton of the thiazoles ring. The HRMS (ESI-MS) compound shows molecular ion peak at $m/z = 369.1022$ (MH^+). Significant attempts were made to synthesize hydrazinyl thiazoles by conventional method using all the aryl ketones employed in the above mentioned green protocol. But the products obtained were only the thiosemicarbazones of the corresponding ketones even after a long reaction time (**8a–d**). However the microwave irradiation not only yields expected thiazoles in short reaction time in many cases but also pure products with very high yields.

5. Conclusion

In summary we have developed a novel and convenient method for the synthesis of a series of heterocyclic compounds possessing biologically potent thiazole nucleus with good to excellent yield and purity.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jscs.2014.05.001>.

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