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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.

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. ^{1}H NMR spectra were recorded at 400 and 500 MHz on a Bruker AMX 400 and 500 MHz spectrophotometer using $CDCl_3$ or 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 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; ^{1}H 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 ($M+H^+$); CHN analysis: $C_{18}H_{17}N_3OS$. 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; ^{1}H 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 ($M+H^+$); CHN analysis: $C_{18}H_{16}N_4O_3S$. 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; ^{1}H NMR (400 MHz, 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 ($M+H^+$); CHN analysis: $C_{19}H_{19}N_3O_2S$. 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; ^{1}H NMR (400 MHz, 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, 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 ($M+H^+$); CHN analysis: $C_{18}H_{16}ClN_3OS$. 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; ^{1}H NMR (400 MHz, 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, 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 ($M+H^+$); CHN analysis: $C_{18}H_{17}N_3O_2S$. 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; ^{1}H NMR (400 MHz, 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, 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 ($M+H^+$); CHN analysis: $C_{17}H_{13}C_{12}N_3S$. 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; ^{1}H NMR (400 MHz, 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, 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 ($M+H^+$); CHN analysis $C_{19}H_{18}ClN_3O_2S$. Anal. Calcd. (%) for: C, 58.83; H, 4.68; N, 10.83; found (%): C, 58.53; H, 4.57; N, 10.73.