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RESEARCH ARTICLE

Microwave Effect versus Thermal Effect on the Synthesis of 4-[(substituted benzylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-Triazole-3-Thiol Candidates

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A series of Schiff base derivatives **4a-k** were synthesized from 4-amino-3-(4-pyridyl)-5-mercapto-4H-1,2,4-triazole **3** as starting materials by using microwave irradiation technique. The synthesized compounds were fully characterized by NMR, FT-IR, elemental analysis, and HR-mass spectra. The results indicated that the microwave irradiation technique gave higher yields of pure products with short time of the reaction in compare to the thermal method.

Keywords: Synthesis, 1,2,4-Triazoles, Schiff Base, Microwave Irradiation.

1. INTRODUCTION

Recently nanotechnology is being applied in the fields of synthesis of single-site catalyst, antimicrobial nanocomposites, also in the field of drug delivery systems and chemical synthesis.[1, 2] Microwave irradiation technique is considering one of the important ways in nanotechnology area especially in the field of chemistry. Microwave irradiation has gained popularity in the past decade as a powerful tool for rapid and efficient synthesis of a variety of compounds.[3] Microwaves are being used as a heat source for chemical synthesis. The fundamental mechanism of microwave heating involves agitation of polar molecules or ions that oscillate under the effect of an oscillating electric or magnetic field.[4] In the presence of an oscillating field, particles try to orient themselves or be in phase with the field. However, the motion of these particles is restricted by resisting forces (inter-particle interaction and electric resistance) which restrict the motion of particles and generate random motion, producing heat.[5]

1,2,4-Triazole moieties have been incorporated into a wide variety of therapeutically interesting drug candidates, alprozolam (tranquilizer), benatraden (diuretic), trapidil (hypotensive), trazodon (antidepressant), anastrozole, letrozole, vorozole (antineoplastic), ribavirin (antiviral)[6] and antimycotic ones such as fluconazole, itraconazole, voriconazole.[7]

The mercapto and thione substituted 1,2,4-triazole ring system have been reported to possess a variety of biological activities such as antibacterial,[8–10] antifungal,[11–13] anticancer,[14, 15] anticonvulsant.[16]

2. RESULTS AND DISCUSSION

In the present work, treatment of isonicotinic hydrazide **(1)** with carbon disulfide, in the presence of potassium hydroxide, afforded the potassium salt of hydrazinecarbodithioate **(2)**. Furthermore, treatment of the salt **(2)** with hydrazine hydrate in aqueous ethanol afforded the corresponding 1,2,4-triazole-5-thione derivative **(3)**.[17] Treatment of the latter compound with substituted aromatic aldehydes in refluxing DMF for 7–9 hrs, in the presence of acetic acid, afforded compounds identified as 4-[(substituted benzylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiols **(4a-k)** (Scheme 1). The obtained above products can be also synthesized by using microwave method. To a mixture of **(3)** (1.93 g, 0.01 mol) and aromatic aldehydes (0.01 mol) in dry DMF (3 mL), one drop of glacial acetic acid was added. The reaction mixture was irradiated in microwave oven for 5–10 min. to afford the corresponding Schiff base derivatives **(4a-k)**, respectively, in a pure form.

Microwave irradiation technique and thermal (traditional) methods were used in the synthesis of 1,2,3-ttiazole Schiff bases. Comparative study on the two methods was

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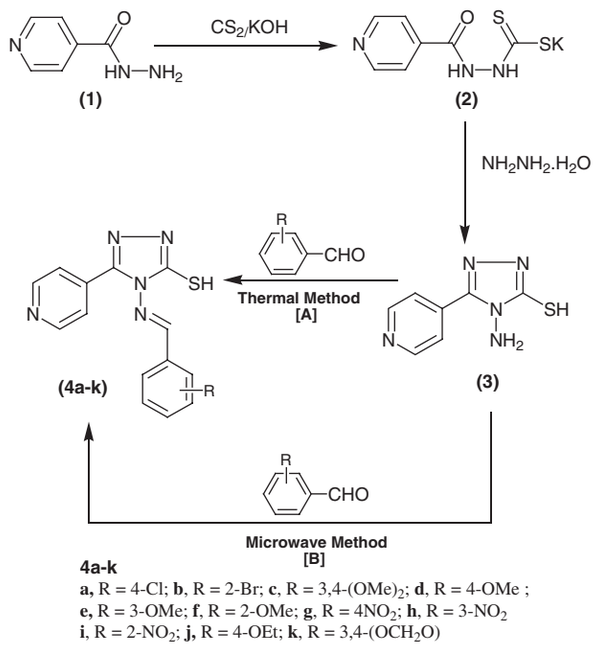

Scheme 1. Synthetic routes for compounds (**4a-k**).

carried out and it was observed that all the reactions under microwave irradiation were completed within 5–10 min. whereas similar reactions under conventional heating at reflux gave poorer yields after much reaction time 7–9 h. The results above in Table I indicated that the microwave irradiation technique gave higher yields of cleaner products in less reaction time from hours to minutes and improves reproducibility in compare the thermal method. The reactions occurred remarkably fast, under mild condition using highly inexpensive domestic microwave oven as the irradiation source. So, microwave irradiation technique is becoming an increasingly popular method for synthetic chemistry due to the minor energy consumption, and environmental compatibility.

Table I. Comparative study between two methods [A] and [B] according to the reaction time and yields of the synthesized compounds (**4a-k**).

	Method (A) thermal (Traditional)		Method (B) microwave		
Comp. no.	% Yield	Reaction time (hrs.)	% Yield	Reaction time (min.)	References
(4a)	44	8	90	5	[18]
(4b)	55	8	87	6	[19]
(4c)	49	9	89	9	[20]
(4d)	60	7	90	8	[20]
(4e)	50	9	60	10	[18]
(4f)	40	8	60	9	–
(4g)	57	8	62	9	–
(4h)	66	8	70	10	–
(4i)	66	8	83	8	–
(4j)	65	7	80	8	–
(4k)	70	9	88	6	–

3. EXPERIMENTAL DETAILS

All the solvents were of LR grade and were obtained from Merck. The elemental analysis (C, H, N and S) of all compounds were performed on the CHNS Elementar (Analysen systeme GmbH, Germany) and Vario EL III (Elementar Americas Corporation) and were within a limit of ±0.4% and ±0.3%, respectively, of the theoretical values. The homogeneity of the compounds was checked by TLC performed on Silica gel G coated plates (Merck). Iodine chamber was used for visualization of TLC spots. The FT-IR spectra were recorded in KBr pellets on a (Spectrum BX) Perkin Elmer FT-IR spectrophotometer. Melting points were determined on a Gallenkamp melting point apparatus, and thermometer was uncorrected. NMR Spectra were scanned in DMSO-d_6 on a Bruker NMR spectrophotometer operating at 500 MHz for ^{1}H and 125.76 MHz for ^{13}C at the Research Center, College of Pharmacy, King Saud University, Saudi Arabia. Chemical shifts are expressed in δ-values (*ppm*) relative to TMS as an internal standard and D_2O was added to confirm the exchangeable protons. Mass spectra were measured on Jeol-JMS-700 HR-MS. Microwave irradiations were carried out using a domestic microwave oven LG-MS-2044 W/OO, frequency is 2450 MHz and operating at 420 watts of the total power.

3.1. Synthesis of 4-Amino-3-(4-pyridyl)-5-Mercapto-4H-1,2,4-Triazole (3)

To a mixture of isonicotinic acid hydrazide **(1)** (13.7 g, 0.1 mol) and potassium hydroxide (11.2 g, 0.1 mol) in absolute ethanol (200 mL), carbon disulfide (12.5 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 16 hrs, and then diethyl ether (100 mL) was added to the reaction mixture and then stirred for 3 hrs. Diethyl ether was separated, evaporated to dryness to afford dithiocarbazinate salt **(2)**. To a solution of **(2)** (0.01 mol) in water (100 mL), hydrazine hydrate (99%) (10.3 g, 0.1 mol) was added gradually with stirring and the content was refluxed for 8 hrs, during which hydrogen sulfide gas evolved and the color of the reaction mixture changed to deep green. After cooling, the mixture was acidified with hydrochloric acid to pH 1. The yellow colored solid separated out and was filtered off and purified by recrystallization from dimethylformamide to give compound **(3)**.[17]

3.2. Synthesis of Schiff Base Candidates (4a-k)

3.2.1. Method [A]: Thermal Method

A mixture of (4-amino-5-pyridin-4-yl)-4H-1,2,4-triazol-3-thiol **(3)** (1.93 g, 0.01 mol) and appropriate aldehydes, namely, 4-chloro-, 2-bromo-, 3,4-dimethoxy-, 4-methoxy-, 3-methoxy-, 2-methoxy-, 4-nitro-, 3-nitro-, 2-nitro-, 4-ethoxy-benzaldehydes, benzo[d]-[1,3]dioxole-5-carbaldehyde, 2-thiophene-carbaldehyde or 2-furane-carbaldehyde (0.01 mol) in dimethyl formamide (20 mL) and few drops of glacial acetic acid was heated under

reflux for 7–9 hrs. The progress of reaction was monitored by TLC. After cooling, the precipitate obtained was filtered off, dried in vacuum and recrystallized from ethanol to give Schiff base derivatives **(4a-k)**, respectively.

3.2.2. Method [B]: Microwave Irradiation Method

To a mixture of (4-amino-5-pyridin-4-yl)-4H-1,2,4-triazol-3-thiol **(3)** (1.93 g, 0.01 mol) and the appropriate aromatic aldehydes, namely, 4-chloro-, 2-bromo-, 3,4-dimethoxy-, 4-methoxy-, 3-methoxy-, 2-methoxy-, 4-nitro-, 3-nitro-, 2-nitro-, 4-ethoxy-, benzaldehydes, benzo[d][1,3]dioxole-5-carbaldehyde, (0.01 mol) in dry DMF (3 mL) with one drop of glacial acetic acid. The reaction mixture was irradiated in microwave oven for 5–10 minutes and then solvent was distilled off under reduced pressure. The obtained solid was triturated and recrystallized from the proper solvents to afford the corresponding Schiff base derivatives **(4a-k)**, respectively, in a pure form. All obtained products were confirmed by comparison with authentic samples which obtained from Method A.

3.2.3. 4-[(4-Chlorobenzylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-Triazole-3-Thiol **(4a)**

mp. 276–278 °C. IR spectrum, ν, cm^{-1}: 3013 (Ar C–H str.), 2568 (S–H str.), 1606 (Ar C═C str.), 1570 (C═N str.), 1317 (C–N str.), 1004 (C–Cl), 601 (C–S str.). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 5.86 (*s*, 1H, N═CH), 7.65–8.77 (*m*, 8H, Ar–H), 14.2 (*s*, 1H, –SH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 167.6, 165.5, 150.3, 137.6, 132.9, 130.6, 129.4, 121.8. Mass spectrum: m/z 315 $[M]^+$. Found, %: C 53.05; H 3.20; N 22.10; S 10.12. $C_{14}H_{10}ClN_5S$. Calculated, %: C 53.25; H 3.19; N 22.18; S 10.15.

3.2.4. 4-[(2-Bromobenzylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-Triazole-3-Thiol **(4b)**

mp. 230–233 °C. IR spectrum, ν, cm^{-1}: 3157 (Ar C–H str.), 2870 (C–OCH_3 str.), 2558 (S–H str.), 1606 (Ar C═C str.), 1570 (C═N str.), 1316 (C–N str.), 1003 (C–Br), 601 (C–S str.). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 5.86 (*s*, 1H, N═CH), 7.57–8.77 (*m*, 8H, Ar–H), 14.19 (*s*, 1H, –SH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 167.6, 150.1, 147.3, 132.9, 122.2, 121.5. Mass spectrum: m/z 360 $[M]^+$. Found, %: C 46.78; H 2.81; N 19.52; S 8.92. $C_{14}H_{10}BrN_5S$. Calculated, %: C 46.68; H 2.80; N 19.44; S 8.90.

3.2.5. 4-[(3,4-Dimethoxybenzylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-Triazole-3-Thiol **(4c)**

mp. 220–222 °C. IR spectrum, ν, cm^{-1}: 3158 (Ar C–H str.), 2870 (C–OCH_3 str.), 2572 (S–H str.), 1606 (Ar C═C str.), 1570 (C═N str.), 1316 (C–N str.), 601 (C–S str.). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 3.5 (*s*, 6H, –OCH_3), 5.86 (*s*, 1H, N═CH), 8.02–8.77 (*m*, 7H, Ar–H), 14.1 (*s*, 1H, –SH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 167.6, 150.1, 147.3, 132.9, 121.9. Mass spectrum: m/z 312 $[M]^+$. Found, %: C 56.49; H 4.42; N 20.43; S 9.36. $C_{16}H_{15}N_5O_2S$. Calculated, %: C 56.29; H 4.43; N 20.51; S 9.39.

3.2.6. 4-[(4-Methoxybenzylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-Triazole-3-Thiol **(4d)**

mp. 240–242 °C. IR spectrum, ν, cm^{-1}: 3160 (Ar C–H str.), 2870 (C–OCH_3 str.), 2559 (S–H str.), 1606 (Ar C═C str.), 1570 (C═N str.), 1316 (C–N str.), 601 (C–S str.). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 3.49 (*s*, 3H, –OCH_3), 5.86 (*s*, 1H, N═CH), 7.1–8.76 (*m*, 8H, Ar–H), 14.1 (*s*, 1H, –SH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 167.6, 163.1, 150.2, 147.3, 132.9, 131.7, 124, 121.6, 114.7, 55.5. Mass spectrum: m/z 312 $[M]^+$. Found, %: C 57.66; H 4.22; N 22.55; S 10.33. $C_{15}H_{13}N_5OS$. Calculated, %: C 57.86; H 4.21; N 22.49; S 10.30.

3.2.7. 4-[(3-Methoxybenzylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-Triazole-3-Thiol **(4e)**

mp. 265–268 °C; IR spectrum, ν, cm^{-1}: 3100 (Ar C–H str.), 2870 (C–OCH_3 str.), 2560 (S–H str.), 1606 (Ar C═C str.), 1570 (C═N str.), 1317 (C–N str.), 601 (C–S str.). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 3.47 (*s*, 3H, –OCH_3), 5.86 (*s*, 1H, N═CH), 7.2–8.87 (*m*, 8H, Ar–H), 14.2 (*s*, 1H, –SH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 167.7, 159.7, 150.2, 132.9, 121.8, 112.9. Mass spectrum: m/z 312 $[M]^+$. Found, %: C 57.96; H 4.20; N 22.41; S 10.27. $C_{15}H_{13}N_5OS$. Calculated, %: C 57.86; H 4.21; N 22.49; S 10.30.

3.2.8. 4-[(2-Methoxybenzylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-Triazole-3-Thiol **(4f)**

mp. 220–222 °C. IR spectrum, ν, cm^{-1}: 3150 (Ar C–H str.), 2870 (C–OCH_3 str.), 2560 (S–H str.), 1606 (Ar C═C str.), 1570 (C═N str.), 1316 (C–N str.), 601 (C–S str.). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 3.48 (*s*, 3H, –OCH_3), 5.86 (*s*, 1H, N═CH), 7.2–8.86 (*m*, 8H, Ar–H), 14.1 (*s*, 1H, –SH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 167.6, 160.1, 150.2, 145.3, 132.9, 130.7, 123, 121.5, 114.0, 55.0. Mass spectrum: m/z 312 $[M]^+$. Found, %: C 57.65; H 4.21; N 22.54; S 10.34. $C_{15}H_{13}N_5OS$. Calculated, %: C 57.86; H 4.21; N 22.49; S 10.30.

3.2.9. 4-[(4-Nitrobenzylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-Triazole-3-Thiol **(4g)**

mp. 258–260 °C; IR spectrum, ν, cm^{-1}: 3033 (Ar C–H str.), 2582 (S–H str.), 1607 (Ar C═C str.), 1520 (C═N str.), 1546, 1344 (Ar NO_2 str.), 1315 (C–N str.), 601 (C–S str.). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 5.86 (*s*, 1H, N═CH), 7.7–8.7 (*m*, 8H, Ar–H), 14.1 (*s*, 1H, –SH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 167.6, 150.3, 147.3, 132.9, 129.9, 124.3, 121.5, 119. Mass

spectrum: m/z 226 $[M]^+$. Found, %: C 51.45; H 3.00; N 25.70; S 9.78. $C_{14}H_{10}N_6O_2S$. Calculated, %: C 51.53; H 3.09; N 25.75; S 9.83.

3.2.10. 4-[(3-Nitrobenzylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-Triazole-3-Thiol(4h)

mp. 288–290 °C. IR spectrum, ν, cm^{-1}: 3100 (Ar C–H str.), 2500 (S–H str.), 1607 (Ar C═C str.), 1522 (C═N str.), 1559, 1350 (Ar NO_2 str.), 1315 (C–N str.), 601 (C–S str.). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 5.89 (s, 1H, N═CH), 7.0–8.7 (m, 8H, Ar–H), 14.1 (s, 1H, –SH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 167.7, 150.6, 147.3, 134.8, 132.0, 130.0, 128.0, 123.0, 121.0, 119. Mass spectrum: m/z 326 $[M]^+$. Found, %: C 51.63; H 3.08; N 25.65; S 9.80. $C_{14}H_{10}N_6O_2S$. Calculated, %: C 51.53; H 3.09; N 25.75; S 9.83.

3.2.11. 4-[(2-Nitrobenzylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-Triazole-3-Thiol (4i)

mp. 243–245 °C. IR spectrum, ν, cm^{-1}: 3157 (Ar C–H str.), 2574 (S–H str.), 1606 (Ar C═C str.), 1570 (C═N str.), 1516, 1449 (Ar NO_2 str.), 1316 (C–N str.), 601 (C–S str.). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 5.85 (s, 1H, N═CH), 8.0–8.8 (m, 8H, Ar–H), 14.19 (s, 1H, –SH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 167.6, 150.1, 147.4, 132.9, 121.6. Mass spectrum: m/z 327 $[M]^+$. Found, %: C 51.43; H 3.10; N 25.80; S 9.81. $C_{14}H_{10}N_6O_2S$. Calculated, %: C 51.53; H 3.09; N 25.75; S 9.83.

3.2.12. 4-[(4-Ethoxybenzylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-Triazole-3-Thiol (4j)

mp. 265–267 °C. IR spectrum, ν, cm^{-1}: 3158 (Ar C–H str.), 2558 (S–H str.), 1606 (Ar C═C str.), 1570 (C═N str.), 1316 (C–N str.), 601 (C–S str.). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 1.3 (s, 3H, CH_3), 4.1 (s, 2H, –OCH_2), 5.87 (s, 1H, N═CH), 7.1–8.7 (m, 8H, Ar–H), 14.18 (s, 1H, –SH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 167.7, 162.4, 150.2, 147.3, 132.9, 130.9, 123, 121.0, 115.0, 63, 30, 21, 14. Mass spectrum: m/z 325 $[M]^+$. Found, %: C 59.26; H 4.66; N 21.60; S 9.82. $C_{16}H_{15}N_5OS$. Calculated, %: C 59.06; H 4.65; N 21.52; S 9.58.

3.2.13. 4-[(1,3-Benzodioxol-5-ylmethylidene)amino]-5-(pyridin-4-yl)-4H-1,2,4-Triazole-3-Thiol (4k)

mp. 235–237 °C. IR spectrum, ν, cm^{-1}: 3150 (Ar C–H str.), 2582 (S–H str.), 1607 (Ar C═C str.), 1570 (C═N str.), 1317 (C–N str.), 601 (C–S str.). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 2.53 (s, 2H, CH_2), 5.86 (s, 1H, N═CH), 8.0–8.7 (m, 7H, Ar–H), 14.1 (s, 1H, –SH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 167.6, 150.1, 147.3, 132.9, 121.5. Mass spectrum: m/z 325 $[M]^+$. Found: C 55.28; H 3.42; N 21.47; S 9.83. $C_{15}H_{11}N_5O_2S$. Calculated, %: C 55.38; H 3.41; N 21.53; S 9.86.

4. CONCLUSION

A series of triazole Schiff base derivatives **4a-k** were synthesized by using 4-amino-3-(4-pyridyl)-5-mercapto-4H-1,2,4-triazole **3** as starting materials. Also, microwave irradiation technique was used in the synthesis of these candidates. The synthesized compounds were fully characterized by NMR, FT-IR, elemental analysis, and HR-mass spectra. The results indicated that the microwave irradiation technique gave higher yields of pure products with short time of the reaction in compare to the thermal method.

RESEARCH ARTICLE

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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