Hindawi Publishing Corporation
Journal of Chemistry
Volume 2015, Article ID 593738, 7 pages
http://dx.doi.org/10.1155/2015/593738

Research Article

Reaction of Nitrilimines with Pyruvaldehyde Hydrazones: Synthesis and Antimicrobial Evaluation of Some New 1,2,4-Triazole Derivatives

Hany M. Dalloul

Department of Chemistry, Faculty of Applied Science, Al-Aqsa University of Gaza, P.O. Box 4051, Gaza 76888, State of Palestine

Correspondence should be addressed to Hany M. Dalloul; hmdalloul60@yahoo.com

Received 2 December 2014; Accepted 14 February 2015

Academic Editor: Sevgi Kolaylı

A new series of 1,3,4,5,5-pentasubstituted-1,2,4-triazoles (**4a–j**, **6a–j**) have been synthesized by the 1,3-dipolar cycloaddition of suitable nitrilimines **2** to pyruvaldehyde (2-oxopropanal) hydrazones having (COPh, COOMe, COOEt, Me/Me, and Me/Ph) groups **3** and **5**. Both analytical and spectroscopical data of all the synthesized compounds are in full agreement with the proposed structures. The microbial features of the synthesized compounds were studied by a known method.

1. Introduction

The synthesis of heterocycles has received considerable attention in recent years. 1,2,4-Triazoles and their derivatives constitute an important class of organic compounds with diverse agricultural, industrial, and biological activities [1–3] including antimicrobial [4, 5] sedative, anticonvulsant [6], and anti-inflammatory properties [7], and, consequently, the synthesis of compounds containing 1,2,4-triazole rings in their structure has attracted widespread attention. 1,3-Dipolar cycloaddition is one of the most versatile methods for the construction of five-membered heterocycles [8, 9]. Recently, we have described a versatile and efficient one-pot synthesis of dispiroheterocycles containing 1,2,4-triazole moieties utilizing available ketooximes, hydrazones, and hydrazonoyl halides [10]. Keeping this observation in view and in continuation of our study on the synthesis of biologically active nitrogen containing heterocycles [11–16], this paper presents the synthesis of a series of some new substituted 1,2,4-triazoles via reaction of nitrilimines **2** with different pyruvaldehyde hydrazones **3** and **5**, in anticipation of expected interesting biological activities.

2. Experimental

2.1. Instruments and Reagents. Melting points were determined on an A. Krüss Melting Point Meter and are uncorrected. The IR spectra were measured as potassium bromide pellets using a Satellite 3000 Mid infrared spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 MHz spectrometer at room temperature in DMSO-d_6 solution using tetramethylsilane (TMS) as internal reference. Chemical shifts were recorded as δ values in parts per million (ppm) downfield from internal TMS. Electron impact (EI) mass spectra were run on Shimadzu GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were performed at the Microanalytical Center of Cairo University, Egypt. The hydrazonoyl halides **1** [17–19] and pyruvaldehyde hydrazones **3** and **5** [20] were prepared according to literature procedures. Pyruvaldehyde, tetrahydrofuran (THF), and triethylamine were purchased from Avocado Research Chemicals, England, and used without further purification.

*2.2. Reaction of Nitrilimine **2** with Pyruvaldehyde Hydrazones **3** (General Procedure).* Triethylamine (1.5 g, 15 mmol) was added to the stirred mixture of pyruvaldehyde hydrazones

3 (7.5–10 mmol) and the appropriate hydrazonoyl halides **1** (5 mmol) in dioxane (50 mL) at room temperature and stirring was continued or refluxed for 12–16 hours. The precipitated salt was filtered off and the solvent was then evaporated under reduced pressure. The residue was washed with water (3 × 20 mL), and in few cases the oily or gummy products were triturated with ethanol or methanol (10 mL). The crude solid product was then collected and recrystallized from ethanol or methanol to give the desired compounds **4a–j**.

The following compounds were synthesized using this method.

*2.2.1. 3-Acetyl-4-benzoylamino-5-methyl-1-phenyl-1,2,4-triazole-5-carbaldehyde (**4a**).* Yield 64%; mp. 163–165°C; ^{1}H NMR (DMSO-d_6) δ/ppm 9.73 (1H, s, NH), 8.64 (1H, s, H-C=O), 7.76–7.14 (10H, m, arom. H), 2.56 (3H, s, $COCH_3$), 1.92 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.6 (C=O acetyl), 168.8 (N-C=O), 162.7 (H-C=O), 147.6 (C=N), 143.7–117.9 (8 arom. C.), 90.1 (C-5), 24.2 (CH_3), 23.8 (CH_3 acetyl); IR (KBr) ν/cm^{-1} 3256 (NH), 1691 (C=O), 1682 (H-C=O), 1676 (N-C=O), 1622 (C=N) cm^{-1}; MS: m/z = 350 [M$^+$]; Analysis (% Calculated/found) for $C_{19}H_{18}N_4O_3$ (Mw 350.38) C: 65.13/65.45, H: 5.18/4.90, N: 15.99/16.15.

*2.2.2. 3-Acetyl-1-(4-chlorophenyl)-4-ethoxycarbonylamino-5-methyl-1,2,4-triazole-5-carbaldehyde (**4b**).* Yield 65%; mp. 146–148°C; ^{1}H NMR (DMSO-d_6) δ/ppm 8.72 (1H, s, H-C=O), 6.96 (1H, s, NH), 7.39–7.17 (4H, m, arom. H), 2.69 (2H, q, *J* 7.5, CH_2), 2.54 (3H, s, $COCH_3$), 1.90 (3H, s, CH_3), 1.08 (3H, t, *J* 7.5, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.3 (C=O acetyl), 162.8 (H-C=O), 158.1 (N-C=O), 147.5 (C=N), 143.4–121.3 (4 arom. C.), 89.9 (C-5), 63.2 (CH_2), 24.2 (CH_3), 23.8 (CH_3 acetyl), 14.8 (CH_3 ethyl); IR (KBr) ν/cm^{-1} 3255 (NH), 1730 (O-C=O), 1694 (C=O), 1687 (H-C=O), 1629 (C=N) cm^{-1}; MS: m/z = 352/354 [M$^+$]; Analysis (% Calculated/found) for $C_{15}H_{17}ClN_4O_4$ (Mw 352.87) C: 51.07/50.85, H: 4.86/4.70, N: 15.88/16.05.

*2.2.3. 3-Acetyl-1-(4-chlorophenyl)-4-methoxycarbonylamino-5-methyl-1,2,4-triazole-5-carbaldehyde (**4c**).* Yield 70%; mp. 152–154°C; ^{1}H NMR (DMSO-d_6) δ/ppm 8.71 (1H, s, H-C=O), 6.93 (1H, s, NH), 7.30–7.12 (4H, m, arom. H), 3.68 (3H, s, OCH_3), 2.56 (3H, s, $COCH_3$), 1.91 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.8 (C=O acetyl), 162.5 (H-C=O), 158.3 (N-C=O), 147.3 (C=N), 142.9–120.9 (4 arom. C.), 90.0 (C-5), 53.4 (OCH_3), 24.2 (CH_3), 23.5 (CH_3 acetyl); IR (KBr) ν/cm^{-1} 3275 (NH), 1735 (O-C=O), 1692 (C=O), 1682 (H-C=O), 1626 (C=N) cm^{-1}; MS: m/z = 338/340 [M$^+$]; Analysis (% Calculated/found) for $C_{14}H_{15}ClN_4O_4$ (Mw 338.875) C: 49.64/49.40, H: 4.46/4.60, N: 16.54/16.40.

*2.2.4. 3-Benzoyl-4-benzoylamino-1-(4-chlorophenyl)-5-methyl-1,2,4-triazole-5-carbaldehyde (**4d**).* Yield 66%; mp. 189–191°C; ^{1}H NMR (DMSO-d_6) δ/ppm 9.43 (1H, s, NH), 8.55 (1H, s, H-C=O), 8.12–7.15 (14H, m, arom. H), 1.86 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 184.3 (C=O benzoyl), 168.8 (N-C=O), 162.6 (H-C=O), 147.1 (C=N), 141.3–118.7 (12 arom. C.), 89.1 (C-5), 24.2 (CH_3); IR (KBr) ν/cm^{-1} 3257 (NH), 1682 (H-C=O), 1673 (N-C=O), 1656 (C=O), 1612 (C=N) cm^{-1}; MS: m/z = 446/448 [M$^+$]; Analysis (% Calculated/found) for $C_{24}H_{19}ClN_4O_3$ (Mw 446.90) C: 64.50/64.25, H: 4.29/4.45, N: 7.60/7.45.

*2.2.5. 4-Methoxycarbonylamino-5-methyl-1-phenyl-3-phenylaminocarbonyl-1,2,4-triazole-5-carbaldehyde (**4e**).* Yield 71%; mp. 199–201°C; ^{1}H NMR (DMSO-d_6) δ/ppm 10.43 (1H, s, PhNH), 8.53 (1H, s, H-C=O), 7.72–7.18 (10H, m, arom. H), 6.93 (1H, s, NH), 3.67 (3H, s, OCH_3), 1.91 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 166.4 (PhNH-C=O), 162.6 (H-C=O), 158.4 (N-C=O), 147.6 (C=N), 143.2–115.7 (8 arom. C.), 89.2 (C-5), 53.4 (OCH_3), 24.3 (CH_3); IR (KBr) ν/cm^{-1} 3362 (PhNH), 3257 (NH), 1682 (H-C=O), 1732 (O-C=O), 1655 (C=O), 1618 (C=N) cm^{-1}; MS: m/z = 365 [M$^+$]; Analysis (% Calculated/found) for $C_{19}H_{19}N_5O_3$ (Mw 365.39) C: 62.46/62.25, H: 5.24/5.35, N: 19.17/19.05.

*2.2.6. 1-(4-Bromophenyl)-4-benzoylamino-5-methyl-3-phenylaminocarbonyl-1,2,4-triazole-5-carbaldehyde (**4f**).* Yield 74%; mp. 204–206°C; ^{1}H NMR (DMSO-d_6) δ/ppm 10.46 (1H, s, PhNH), 9.53 (1H, s, NH), 8.52 (1H, s, H-C=O), 7.76–7.21 (14H, m, arom. H), 1.87 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 168.5 (N-C=O), 166.4 (PhNH-C=O), 162.6 (H-C=O), 147.3 (C=N), 143.1–120.7 (12 arom. C.), 88.7 (C-5), 24.2 (CH_3); IR (KBr) ν/cm^{-1} 3365 (PhNH), 3270 (NH), 1689 (H-C=O), 1675 (N-C=O), 1650 (C=O), 1619 (C=N) cm^{-1}; MS: m/z = 506/508 [M$^+$]; Analysis (% Calculated/found) for $C_{24}H_{20}BrN_5O_3$ (Mw 506.36) C: 56.93/57.20, H: 3.98/4.15, N: 13.83/13.70.

*2.2.7. 4-Benzoylamino-1-(4-fluorophenyl)-5-methyl-3-phenylaminocarbonyl-1,2,4-triazole-5-carbaldehyde (**4g**).* Yield 72%; mp. 216–218°C; ^{1}H NMR (DMSO-d_6) δ/ppm 10.71 (1H, s, PhNH), 9.62 (1H, s, NH), 8.65 (1H, s, H-C=O), 7.76–7.16 (14H, m, arom. H), 1.93 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 168.8 (N-C=O), 166.7 (PhNH-C=O), 162.6 (H-C=O), 147.5 (C=N), 143.4–115.7 (12 arom. C.), 89.6 (C-5), 24.5 (CH_3); IR (KBr) ν 3360 (PhNH), 3258 (NH), 1691 (H-C=O), 1678 (N-C=O), 1655 (C=O), 1622 (C=N) cm^{-1}; MS: m/z = 445/447 [M$^+$]; Analysis (% Calculated/found) for $C_{24}H_{20}FN_5O_3$ (Mw 445.46) C: 64.71/64.45, H: 4.53/4.70, N: 15.72/15.55.

*2.2.8. 4-Benzoylamino-1-(4-clorophenyl)-3-(2-furoyl)-5-methyl-1,2,4-triazole-5-carbaldehyde (**4h**).* Yield 65%; mp. 165–167°C; ^{1}H NMR (DMSO-d_6) δ/ppm 9.35 (1H, s, NH), 8.68 (1H, s, H-C=O), 8.31–7.20 (12H, m, arom. H), 1.86 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 173.7 (C=O), 169.0 (N-C=O), 162.6 (H-C=O), 146.8 (C=N), 144.4–115.4 (12 arom. C.), 89.7 (C-5), 24.1 (CH_3); IR (KBr) ν/cm^{-1} 3272 (NH), 1686 (H-C=O), 1676 (N-C=O), 1660 (C=O), 1609 (C=N) cm^{-1}; MS: m/z = 436/438 [M$^+$]; Analysis (% Calculated/found) for $C_{22}H_{17}ClN_4O_4$ (Mw 436.86) C: 60.49/60.25, H: 3.92/4.10, N: 12.82/13.70.

*2.2.9. 4-Benzoylamino-1-(4-clorophenyl)-5-methyl-3-(2-thenoyl)-1,2,4-triazole-5-carbaldehyde (**4i**).* Yield 63%; mp. 176–178°C; ^{1}H NMR (DMSO-d_6) δ/ppm 9.23 (1H, s, NH), 8.53 (1H, s, H-C=O), 8.26–7.15 (12H, m, arom. H), 1.88 (3H, s, $COCH_3$); ^{13}C NMR (DMSO-d_6) δ/ppm 174.6 (C=O), 168.7 (N-C=O), 162.6 (H-C=O), 146.6 (C=N), 144.6–114.9 (12 arom. C.), 89.4 (C-5), 24.0 (CH_3); IR (KBr) ν/cm^{-1} 3275 (NH), 1687 (H-C=O), 1678 (N-C=O), 1665 (C=O), 1612 (C=N) cm^{-1}; MS: m/z = 452/454 [M$^+$]; Analysis (% Calculated/found) for $C_{22}H_{17}ClN_4O_3S$ (Mw 452.92) C: 58.34/58.60, H: 3.78/3.65, N: 12.37/12.50.

*2.2.10. 4-Benzoylamino-1-(4-clorophenyl)-5-methyl-3-(2-naphthoyl)-1,2,4-triazole-5-carbaldehyde (**4j**).* Yield 58%; mp. 186–188°C; ^{1}H NMR (DMSO-d_6) δ/ppm 9.62 (1H, s, NH), 8.64 (1H, s, H-C=O), 8.76–7.24 (16H, m, arom. H), 1.82 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 184.5 (C=O naphthoyl), 168.8 (N-C=O), 162.6 (H-C=O), 146.8 (C=N), 141.4–119.3 (18 arom. C.), 88.7 (C-5), 23.8 (CH_3); IR (KBr) ν/cm^{-1} 3225 (NH), 1687 (H-C=O), 1675 (N-C=O), 1640 (C=O), 1621 (C=N) cm^{-1}; MS: m/z = 496/498 [M$^+$]; Analysis (% Calculated/found) for $C_{28}H_{21}ClN_4O_3$ (Mw 496.96) C: 68.67/68.40, H: 4.26/4.45, N: 11.27/11.15.

*2.3. Reaction of Nitrilimine **2** with Pyruvaldehyde Hydrazones **5** (General Procedure).* Triethylamine (10 mmol) in THF (10 mL) was slowly added to the stirred mixture of pyruvaldehyde hydrazones **5** (5 mmol) and the appropriate hydrazonoyl halides **1** (5 mmol) in THF (50 mL) at room temperature and then refluxed for 12 hours. The cooled and precipitated salt was filtered off, and the solvent was then evaporated under reduced pressure. The residue was washed with water (2 × 25 mL), and in few cases the oily or gummy products were triturated with ethanol or methanol (10 mL). The crude solid product was collected and recrystallized from ethanol or methanol to give the desired compounds.

The following compounds were synthesized using this method.

*2.3.1. 3-Acetyl-4-dimethylamino-5-methyl-1-phenyl-1,2,4-triazole-5-carbaldehyde (**6a**).* Yield 77%; mp. 133–135°C; ^{1}H NMR (DMSO-d_6) δ/ppm 8.63 (1H, s, H-C=O), 7.76–7.14 (4H, m, arom. H), 3.25 (6H, s, $2CH_3$) 2.56 (3H, s, $COCH_3$), 1.92 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.6 (C=O acetyl), 162.8 (H-C=O), 147.8 (C=N), 142.7–117.9 (4 arom. C.), 90.1 (C-5), 43.2 ($2CH_3$), 24.2 (CH_3), 23.8 (CH_3 acetyl); IR (KBr) ν/cm^{-1} 1696 (C=O), 1686 (H-C=O), 1628 (C=N) cm^{-1}; MS: m/z = 274 [M$^+$]; Analysis (% Calculated/found) for $C_{14}H_{17}N_4O_2$ (Mw 274.33) C: 61.30/61.45, H: 6.61/6.77, N: 20.42/20.25.

*2.3.2. 3-Acetyl-1-(4-chlorophenyl)-4-dimethylamino-5-methyl-1,2,4-triazole-5-carbaldehyde (**6b**).* Yield 75%; mp. 141–143°C; ^{1}H NMR (DMSO-d_6) δ/ppm 8.62 (1H, s, H-C=O), 7.39–7.17 (4H, m, arom. H), 3.25 (6H, s, $2CH_3$), 2.54 (3H, s, $COCH_3$), 1.90 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.3 (C=O acetyl), 162.8 (H-C=O), 148.0 (C=N), 142.4–120.9 (4 arom. C.), 89.9 (C-5), 43.2 ($2CH_3$), 24.1 (CH_3), 23.6 (CH_3 acetyl); IR (KBr) ν/cm^{-1} 1696 (C=O), 1688 (H-C=O), 1630 (C=N) cm^{-1}; MS: m/z = 308/310 [M$^+$]; Analysis (% Calculated/found) for $C_{15}H_{17}ClN_4O_2$ (Mw 308.77) C: 54.46/54.75, H: 5.55/5.38, N: 18.15/18.05.

*2.3.3. 3-Acetyl-1-(4-chlorophenyl)-4-methylphenylamino-5-methyl-1,2,4-triazole-5-carbaldehyde (**6c**).* Yield 76%; mp. 122–124°C; ^{1}H NMR (DMSO-d_6) δ/ppm 8.60 (1H, s, H-C=O), 7.30–7.12 (9H, m, arom. H), 3.18 (3H, s, CH_3), 2.56 (3H, s, $COCH_3$), 1.91 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.8 (C=O acetyl), 162.5 (H-C=O), 147.9 (C=N), 142.6–120.5 (8 arom. C.), 90.0 (C-5), 43.4 (CH_3), 24.3 (CH_3), 23.1 (CH_3 acetyl); IR (KBr) ν/cm^{-1} 1697 (C=O), 1684 (H-C=O), 1628 (C=N) cm^{-1}; MS: m/z = 370/372 [M$^+$]; Analysis (% Calculated/found) for $C_{19}H_{19}ClN_4O_2$ (Mw 370.84) C: 61.54/61.27, H: 5.16/4.98, N: 15.11/14.95.

*2.3.4. 3-Benzoyl-1-(4-chlorophenyl)-4-dimethylamino-5-methyl-1,2,4-triazole-5-carbaldehyde (**6d**).* Yield 71%; mp. 159–161°C; ^{1}H NMR (DMSO-d_6) δ/ppm 8.52 (1H, s, H-C=O), 8.12–7.15 (9H, m, arom. H), 3.21 (6H, s, $2CH_3$), 1.86 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 184.3 (C=O benzoyl), 162.6 (H-C=O), 147.1 (C=N), 141.3–118.7 (8 arom. C.), 89.7 (C-5), 43.5 ($2CH_3$), 24.2 (CH_3); IR (KBr) ν/cm^{-1} 1685 (H-C=O), 1660 (C=O), 1623 (C=N) cm^{-1}; MS: m/z = 370/372 [M$^+$]; Analysis (% Calculated/found) for $C_{19}H_{19}ClN_4O_2$ (Mw 370.84) C: 61.54/61.35, H: 5.16/5.30, N: 15.11/15.25.

*2.3.5. 4-Dimethylamino-5-methyl-1-phenyl-3-phenylaminocarbonyl-1,2,4-triazole-5-carbaldehyde (**6e**).* Yield 66%; mp. 189–181°C; ^{1}H NMR (DMSO-d_6) δ/ppm 10.43 (1H, s, PhNH), 8.55 (1H, s, H-C=O), 8.12–7.15 (10H, m, arom. H), 3.12 (6H, s, $2CH_3$), 1.86 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 167.8 (N-C=O), 166.6 (PhNH-C=O), 162.6 (H-C=O), 147.1 (C=N), 142.3–118.7 (8 arom. C.), 88.7 (C-5), 43.0 ($2CH_3$), 24.4 (CH_3); IR (KBr) ν/cm^{-1} 3363 (PhNH), 1687 (H-C=O), 1655 (C=O), 1622 (C=N) cm^{-1}; MS: m/z = 351 [M$^+$]; Analysis (% Calculated/found) for $C_{19}H_{21}N_5O_2$ (Mw 351.41) C: 64.94/65.22, H: 6.02/5.92, N: 19.93/20.05.

*2.3.6. 1-(4-Bromophenyl)-4-dimethylamino-5-methyl-3-phenylaminocarbonyl-1,2,4-triazole-5-carbaldehyde (**6f**).* Yield 64%; mp. 194–196°C; ^{1}H NMR (DMSO-d_6) δ/ppm 10.42 (1H, s, PhNH), 8.52 (1H, s, H-C=O), 7.76–7.21 (9H, m, arom. H), 3.14 (6H, s, $2CH_3$), 1.87 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 167.5 (N-C=O), 166.5 (PhNH-C=O), 162.6 (H-C=O), 147.6 (C=N), 143.1–120.9 (8 arom. C.), 89.8 (C-5), 43.1 ($2CH_3$), 24.3 (CH_3); IR (KBr) ν/cm^{-1} 3365 (PhNH), 1689 (H-C=O), 1650 (C=O), 1629 (C=N) cm^{-1}; MS: m/z = 392/394 [M$^+$]; Analysis (% Calculated/found) for $C_{24}H_{22}BrN_5O_2$ (Mw 492.38) C: 58.55/58.37, H: 4.50/4.35, N: 14.22/14.30.

*2.3.7. 1-(4-Flourophenyl)-5-methyl-4-methylphenylamino-3-phenylaminocarbonyl-1,2,4-triazole-5-carbaldehyde (**6g**).* Yield 68%; mp. 176–178°C; ^{1}H NMR (DMSO-d_6) δ/ppm 10.35 (1H, s, PhNH), 8.57 (1H, s, H-C=O), 7.76–7.16 (14H, m, arom. H), 3.20 (3H, s, CH_3), 1.93 (3H, s, CH_3); ^{13}C NMR

Table 1: Antimicrobial screening results of the tested compounds*.

Comp. number	Antibacterial activity					Antifungal activity	
	Enterococci	*E. coli*	*Staph. aureus*	*Klebsiella* spp.	*Proteus* spp.	*Candida albicans*	*Aspergillus niger*
4a	12	16	14	13	9	13	11
4b	16	16	11	5	12	14	16
4c	17	12	10	12	14	16	15
4d	15	17	15	15	11	14	10
4e	14	15	14	17	10	17	7
4f	12	11	12	16	6	15	8
4g	17	14	10	13	17	13	12
4h	16	12	16	15	7	14	14
4i	14	13	15	11	12	12	10
4j	11	10	13	12	6	11	7
6b	12	12	11	10	11	15	12
6d	9	14	8	12	13	8	14
6g	18	17	16	17	16	17	16
6i	15	13	12	14	12	11	9
DMF	—	—	—	—	—	—	—

*Calculated as average of three values.

(DMSO-d_6) δ/ppm 168.8 (N-C=O), 166.7 (PhNH-C=O), 162.6 (H-C=O), 148.7 (C=N), 143.8–116.1 (12 arom. C.), 89.3 (C-5), 43.7 (N-CH_3), 24.6 (CH_3); IR (KBr) ν/cm^{-1} 3366 (PhNH), 1687 (H-C=O), 1650 (C=O), 1626 (C=N) cm^{-1}; MS: m/z = 431/433 [M^+]; Analysis (% Calculated/found) for $C_{24}H_{22}FN_5O_2$ (Mw 431.47) C: 66.81/66.65, H: 5.14/5.05, N: 16.23/16.34.

*2.3.8. 1-(4-Chlorophenyl)-4-dimethylamino-3-(2-furoyl)-5-methyl-1,2,4-triazole-5-carbaldehyde (**6h**).* Yield 76%; mp. 145–147°C; ^{1}H NMR (DMSO-d_6) δ/ppm 8.61 (1H, s, H-C=O), 8.31–7.20 (7H, m, arom. H), 3.28 (6H, s, 2CH_3), 1.86 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 174.6 (C=O), 162.6 (H-C=O), 147.8 (C=N), 144.9–115.4 (8 arom. C.), 89.7 (C-5), 43.0 (2CH_3), 23.7 (CH_3); IR (KBr) ν/cm^{-1} 1688 (H-C=O), 1655 (C=O), 1619 (C=N) cm^{-1}; MS: m/z = 360/362 [M^+]; Analysis (% Calculated/found) for $C_{17}H_{17}ClN_4O_3$ (Mw 360.80) C: 56.59/56.33, H: 4.75/4.63, N: 15.53/15.70.

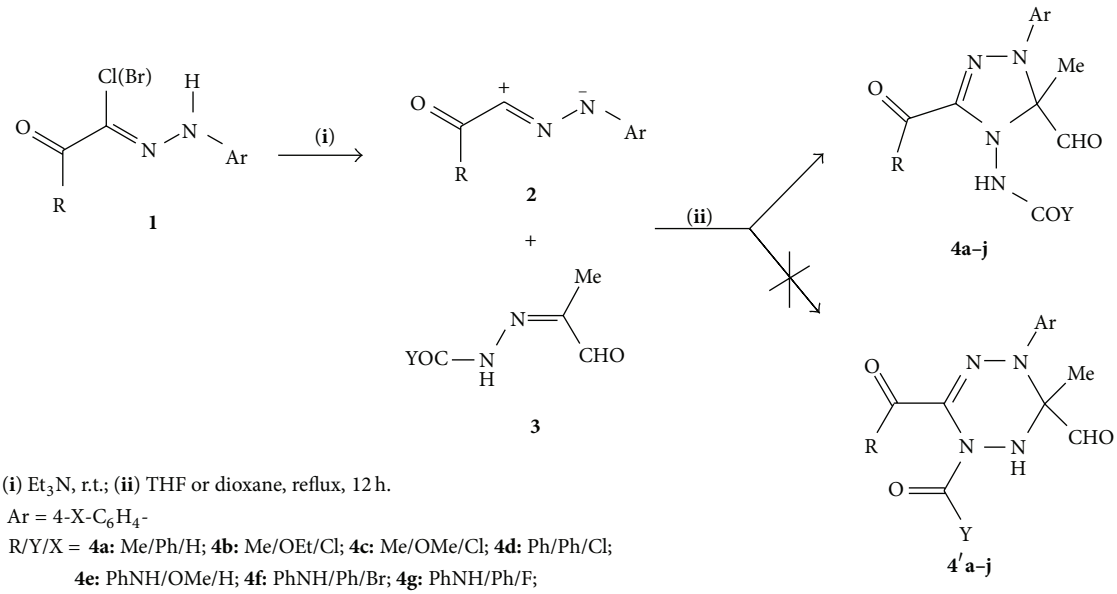
*2.3.9. 1-(4-Chlorophenyl)-4-dimethylamino-5-methyl-3-(2-thenoyl)-1,2,4-triazole-5-carbaldehyde (**6i**).* Yield 73%; mp. 156–158°C; ^{1}H NMR (DMSO-d_6) δ/ppm 8.58 (1H, s, H-C=O), 8.26–7.15 (7H, m, arom. H), 3.25 (6H, s, 2CH_3), 1.88 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 176.2 (C=O), 162.6 (H-C=O), 147.6 (C=N), 144.6–115.3 (8 arom. C.), 89.4 (C-5), 43.2 (2CH_3), 23.8 (CH_3); IR (KBr) ν/cm^{-1} 1686 (H-C=O), 1660 (C=O), 1620 (C=N) cm^{-1}; MS: m/z = 376/378 [M^+]; Analysis (% Calculated/found) for $C_{17}H_{17}ClN_4O_2S$ (Mw 376.87) C: 54.18/54.40, H: 4.55/4.65, N: 14.87/14.75.

*2.3.10. 1-(4-Chlorophenyl)-5-methyl-4-methylphenylamino-3-(2-naphthoyl)-1,2,4-triazole-5-carbaldehyde (**6j**).* Yield 68%; mp. 202–204°C; ^{1}H NMR (DMSO-d_6) δ/ppm 8.60 (1H, s, H-C=O), 8.76–7.24 (16H, m, arom. H), 3.06 (3H, s, CH_3), 1.82 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 183.9 (C=O naphthoyl), 162.2 (H-C=O), 146.8 (C=N), 142.4–120.3 (18 arom. C.), 88.7 (C-5), 42.9 (NCH_3), 23.8 (CH_3); IR (KBr) ν/cm^{-1} 1685 (H-C=O), 1645 (C=O), 1622 (C=N) cm^{-1}; MS: m/z = 482/486 [M^+]; Analysis (% Calculated/found) for $C_{28}H_{23}ClN_4O_2$ (Mw 482.97) C: 69.63/69.40, H: 4.80/4.91, N: 11.60/11.48.

2.4. Antimicrobial Activity Screening. Antimicrobial activity screening of the synthesized compounds was determined by the agar dilution technique as recommended by the Clinical and Laboratory Standard Institute (CLSI) [21]. The tested compounds were dissolved in dimethyl formamide (DMF). An inoculum of about 1.5×10^8 colony forming units per spot was applied to the surfaces of Mueller-Hinton agar plates containing graded concentrations of the respective compounds; plates were incubated at 37°C for 18 h. The spot with the lowest concentration of compound showing no growth was defined as the minimum inhibitory concentration (MIC). All organisms used in this study were standard strains obtained from the Microbiology Laboratory (Al-Aqsa University) and included bacterial strains such as *Enterococci*, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella* spp., and *Proteus* spp. and fungi strains such as *Aspergillus niger* and *Candida albicans*. The MIC of tetracycline and fluconazole was determined concurrently as reference for antibacterial and antifungal activities, respectively (Table 1). Control DMF was carried out with each experiment.

3. Results and Discussion

3.1. Chemistry. 1,3-Dipolar cycloaddition of nitrilimines **2**, generated in situ from hydrazonoyl halides **1** in tetrahydrofuran or 1,4-dioxane in the presence of triethylamine, to 2-oxopropanal hydrazones **3** (Y = COPh, COOMe, and COOEt) was carried out at room temperature for 12 h, leading to the formation of 1,2,4-triazole derivatives **4a**–**j** as



Scheme 1: Synthetic pathway for the preparation of 1,2,4-triazoles **4a–j**.

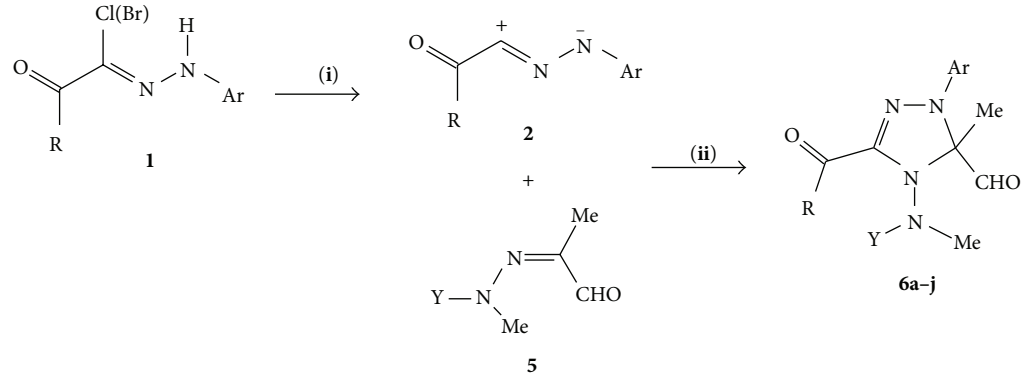
cycloaddition products rather than the cyclocondensation 1,2,4,5-tetrazines **4′a–j** (Scheme 1). It is worth mentioning that the latter products **4′a–j** were obtained from the reaction of hydrazonoyl halides with methyl hydrazones of aliphatic aldehydes and ketones [22]. This can be explained on the basis of the weak nucleophilicity of the nitrogen atom of the hydrazones carrying the electron withdrawing groups in comparison to that of the nitrogen atom carrying methyl group in methyl hydrazones. The purity of obtained compounds was controlled by TLC and elemental analyses. Both the analytical and spectral data (IR, ^{1}H NMR, ^{13}C NMR, and mass spectra) of the synthesized triazoles **4a–j** were in full agreement with the proposed structures and were depicted in Experimental.

The electron impact (EI) mass spectra displayed the correct molecular ions in accordance with the suggested structures. Their IR spectra showed absorption bands in the regions 3275–3225 cm^{-1}, 1690–1680 cm^{-1}, and 1620–1610 cm^{-1} assignable to NH, formyl, and C=N groups, respectively. Their 1H NMR spectra revealed aromatic protons at 8.3–7.1 ppm and singlet signal at 8.7–8.5 ppm assigned to H-C=O proton and singlet signal in the region 1.9-1.8 ppm assignable to the CH_3 proton at quaternary carbon. The detailed ^{1}H NMR data is shown in Experimental. Their 13C NMR spectra showed all the signals corresponding to the proposed structures, especially C-5 (quaternary carbon) which was found to resonate at about 90–85 ppm. This is similar to reported values of quaternary carbon flanked by two nitrogen atoms in five-membered heterocycles [22–24], which provide strong evidence in support of the structures **4a–j** rather than the six-membered heterocyclic structures **4′a–j** which is expected to have a C-6 signal at about 70–65 ppm. The complete ^{13}C NMR data are presented in Experimental.

On the other hand, the reaction of the same nitrilimines **2** with 2-oxopropanal hydrazones **5** having N,N-dimethyl or N-methyl-N-phenyl substituents, under ambient temperature, affords only one isolable product in each case. On the bases of their spectroscopical data, the structures of the reaction products were identified as 1,3,4,5,5-substituted-1,2,4-triazoles **6a–j** (Scheme 2) in good yields.

The synthesized compounds **6a–j** gave satisfactory analysis for the proposed structures which are confirmed on the bases of their spectroscopical data. The electron impact (EI) mass spectra displayed the correct molecular ions (M) in accordance with the suggested structures. Their IR spectra showed absorption bands in the region 1695–1950 cm^{-1} assignable to carbonyl and formyl group. The absorption band of C=N appeared in 1630–1620 cm^{-1} region. Their ^{1}H NMR spectrum revealed characteristic signals for the N-CH_3 at about δ 3.3–3.1 ppm in addition to the signals resulting from the formyl and aromatic hydrogens. ^{13}C NMR spectrum exhibited the characteristic signals of the suggested structures. The signal for quaternary carbon (C-5) appeared around δ 90 ppm. The signal at δ 37.8–37.2 ppm is attributed to the N-CH_3 carbon. The entire ^{13}C NMR data are presented in Experimental.

3.2. Antimicrobial Activity. Most of the synthesized compounds were screened in vitro for their antimicrobial activity against a variety of bacterial strains such as *Enterococci*, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella* spp., and *Proteus* spp. and fungi such as *Aspergillus niger* and *Candida albicans,* employing the nutrient agar disc diffusion method [25, 26] at 10 mg/mL concentration in dimethyl formamide (DMF) used as solvent control, by measuring the average diameter of the inhibition zone in mm. The results showed that all the tested compounds exhibited weak to moderate



(**i**) Et_3N, r.t.; (**ii**) THF or dioxane, reflux, 12 h.

Ar = 4-X-C_6H_4-

R/Y/X = **6a:** Me/Me/H; **6b:** Me/Me/Cl; **6c:** Me/Ph/Cl; **6d:** Ph/Me/Cl;
6e: PhNH/Me/H; **6f:** PhNH/Ph/Br; **6g**: PhNH/Ph/F;
6h: 2-C_4H_3O/Me/Cl; **6i:** 2-C_4H_3S/Me/Cl; **6j:** 2-$C_{10}H_7$/Ph/Cl

Scheme 2: Synthetic pathway for the preparation of triazoles **6a–j**.

degree of activity against bacteria and fungi compared with well-known antibacterial and antifungal substances such as tetracycline and fluconazole, respectively. The results are given in Table 1. According to NCCLS (2004), zones of inhibition for tetracycline and fluconazole <14 mm were considered resistant, between 15 and 18 mm were considered weakly sensitive, and >19 mm were considered sensitive. Also, the results showed the degree of inhibition varied with the tested compounds.

4. Conclusion

In conclusion, the reaction of several nitrilimines with pyruvaldehyde hydrazones having electron withdrawing or electron releasing groups leads to formation of pentasubstituted-1,2,4-triazoles and some of them were found to possess various antimicrobial activities towards all the microorganisms tested. The results confirm that the antimicrobial activity is strongly dependent on the nature of the substituents on triazole rings.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

The author wishes to thank Dr. A. Abu Samaha for screening of the selected synthesized compounds for their antimicrobial activities.

References

[1] N. G. Aher, V. S. Pore, N. N. Mishra et al., "Synthesis and antifungal activity of 1,2,3-triazole containing fluconazole analogues," *Bioorganic & Medicinal Chemistry Letters*, vol. 19, no. 3, pp. 759–763, 2009.

[2] H. Bayrak, A. Demirbas, S. A. Karaoglu, and N. Demirbas, "Synthesis of some new 1,2,4-triazoles, their Mannich and Schiff bases and evaluation of their antimicrobial activities," *European Journal of Medicinal Chemistry*, vol. 44, no. 3, pp. 1057–1066, 2009.

[3] A. K. Jordão, V. F. Ferreira, T. M. L. Souza et al., "Synthesis and anti-HSV-1 activity of new 1,2,3-triazole derivatives," *Bioorganic & Medicinal Chemistry*, vol. 19, no. 6, pp. 1860–1865, 2011.

[4] A. H. El-Masry, H. H. Fahmy, and S. H. Ali Abdelwahed, "Synthesis and antimicrobial activity of some new benzimidazole derivatives," *Molecules*, vol. 5, no. 12, pp. 1429–1438, 2000.

[5] A. S. Orabi, M. A. Moneim, E. El-Din Salem, and M. E.-D. Abd El-Fattah, "Synthesis and physicochemical studies of some antimicrobial active triazole metal complexes," *Polish Journal of Chemistry*, vol. 74, no. 12, pp. 1675–1683, 2000.

[6] A. Almasirad, S. A. Tabatabai, M. Faizi et al., "Synthesis and anticonvulsant activity of new 2-substituted-5-[2-(2- fluorophenoxy)phenyl]-1,3,4-oxadiazoles and 1,2,4-triazoles," *Bioorganic and Medicinal Chemistry Letters*, vol. 14, no. 24, pp. 6057–6059, 2004.

[7] G. Roma, G. C. Grossi, M. Di Braccio, M. Ghia, and F. Mattioli, "1,5-Benzodiazepines IX. A new route to substituted 4*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-5-amines with analgesic and/or anti-inflammatory activities," *European Journal of Medicinal Chemistry*, vol. 26, no. 5, pp. 489–496, 1991.

[8] A. Padwa, "Intremolecular 1,3-dipolar cycloadditions," in *Comprehensive Organic Synthesis*, B. M. Trost and I. Flemin, Eds., vol. 4, pp. 1069–1109, Pergamon, Oxford, UK, 1991.

[9] P. Caramella and P. Grunanger, in *1,3-Dipolar Cycloaddition Chemistry*, A. Padwa, Ed., vol. 1, pp. 291–319, Wiely Interscience, New York, NY, USA, 1984.

[10] H. M. Dalloul and A. S. A. Samaha, "Synthesis of nitrogen-containing dispiroheterocycles using nitrilimines (II)," *Journal of the Serbian Chemical Society*, vol. 75, no. 11, pp. 1473–1479, 2010.

[11] G. Turan-Zitouni, Z. A. Kaplancikli, M. T. Yildiz, P. Chevallet, and D. Kaya, "Synthesis and antimicrobial activity of 4-phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[*N*-(2-thiazolyl)acetamido]thio-4H-1,2,4-triazole derivatives," *European Journal of Medicinal Chemistry*, vol. 40, no. 6, pp. 607–613, 2005.

[12] S. N. Demirbas, A. Demirbas, and S. Alpay-Karaoglu, "Synthesis and biological activities of new 1,2,4-triazol-3-one derivatives," *Russian Journal of Bioorganic Chemistry*, vol. 31, pp. 430–440, 2005.

[13] M. Alkan, H. Yüksek, Ö. Gürsoy-Kol, and M. Calapoğlu, "Synthesis, acidity and antioxidant properties of some novel 3,4-disubstituted-4,5-dihydro-1H-1,2,4-triazol-5-one derivatives," *Molecules*, vol. 13, no. 1, pp. 107–121, 2008.

[14] O. G. Kol and H. Yüksek, "Synthesis and in vitro antioxidant evaluation of some novel 4, 5-dihydro-1H-1, 2, 4-triazol-5-one derivatives," *E-Journal of Chemistry*, vol. 7, no. 1, pp. 123–136, 2010.

[15] O. Bekircan, B. Kahveci, and M. Küçük, "Synthesis and anticancer evaluation of some new unsymmetrical 3,5-diaryl-4H-1,2,4-triazole derivatives," *Turkish Journal of Chemistry*, vol. 30, no. 1, pp. 29–40, 2006.

[16] H. Yüksek, A. Demirbaş, A. Ikizler, C. B. Johansson, C. Çelik, and A. A. Ikizler, "Synthesis and antibacterial activities of some 4,5-dihydro-1H-1,2,4-triazol-5-ones," *Arzneimittel-Forschung/Drug Research*, vol. 47, no. 4, pp. 405–409, 1997.

[17] P. Frohberg, G. Drutkowski, and C. Wagner, "Synthesis and structural assignment of oxanilo-N-arylhydrazonoyl chlorides," *European Journal of Organic Chemistry*, no. 10, pp. 1654–1663, 2002.

[18] A. Shawali, H. M. Hassaneen, A. Shetta, A. Osman, and F. Abdel-Galil, "Regioselectivity of reactions of 2-furoyl-*N*-aryl nitrile imine with some dipolarophiles," *Heterocycles*, vol. 19, no. 1, pp. 57–66, 1982.

[19] M. M. El-Abadelah, A. Q. Hussein, M. R. Kamal, and K. H. Al-Adhami, "Heterocycles from nitrile imines. Part I. 1,2,3,4-tetrahydro-1,2,4,5-tetrazines," *Heterocycles*, vol. 27, no. 4, pp. 917–924, 1988.

[20] M. Begtrup and H. P. Nytoft, "Reactions of glyoxals with hydrazones: a new route to 4-hydroxy-pyrazoles," *Journal of the Chemical Society, Perkin Transactions 1*, pp. 81–86, 1985.

[21] Clinical and Laboratory Standards Institute, "Methods for dilution antimicrobial susceptibility tests for bacteria grow aerobically," Approved Standard M7-A4, Clinical and Laboratory Standards Institute, Wayne, Pa, USA, 2005.

[22] E. A. El-Sawi, A. M. Awadallah, A.-R. S. Ferwanah, and H. M. Dalloul, "Reaction of C-aroyl-N-aryl nitrilimines with selected aliphatic keto-hydrazones and keto-methylhydrazones," *Asian Journal of Chemistry*, vol. 14, no. 3-4, pp. 1225–1229, 2002.

[23] A. M. Awadallah, E. A. El-Sawi, A. R. S. Ferwanah, and H. M. Dalloul, "1,2,4-Triazoles from 1,3-dipolar cycloaddition reaction of nitrilimines with aliphatic ketohydrazones carrying electron withdrawing groups," *Asian Journal of Chemistry*, vol. 14, no. 3-4, pp. 1230–1234, 2002.

[24] A.-R. S. Ferwanah, "1,3-Dipolar cycloaddition reaction of C-acetyl-N-arylnitrilimines with selected aliphatic benzoylhydrazones," *Synthetic Communications*, vol. 33, no. 2, pp. 243–251, 2003.

[25] O. N. Irobi, M. Moo-Young, and W. A. Anderson, "Antimicrobial activity of annatto (*Bixa orellana*) extract," *International Journal of Pharmacognosy*, vol. 34, no. 2, pp. 87–90, 1996.

[26] R. J. Grayer and J. B. Harborne, "A survey of antifungal compounds from higher plants, 1982–1993," *Phytochemistry*, vol. 37, no. 1, pp. 19–42, 1994.