ISSN 1070-3632, Russian Journal of General Chemistry, 2016, Vol. 86, No. 12, pp. 2845–2848. © Pleiades Publishing, Ltd., 2016.

Synthesis and Biological Activity of New 2,6-Diphenyl-4-(1-phenyl-1*H*-1,2,3-triazol-4-yl)pyridines[1]

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Received July 1, 2016

Abstract—An efficient one-pot synthesis of new 2,6-diphenyl-4-(1-phenyl-1*H*-1,2,3-triazol-4-yl)pyridines is presented. This involves the three-component reaction of aldehydes with ketones and ammonium acetate in the presence of catalytic amount of iodine/AcOH. The newly synthesized compounds were characterized by IR, ^{1}H, ^{13}C NMR spectra, and MS data. The products were screened for antibacterial and antifungal activity. Some of the tested compounds exhibited high activity.

Keywords: triazole, aldehydes, 2,6-diphenyl-triazolyl-pyridine, ammonium acetate, iodine, and antimicrobial activity

DOI: 10.1134/S1070363216120483

INTRODUCTION

Pyridine ring system, particularly 2,4,6-triarylpyridine [1, 2] are important synthons in supra molecular chemistry due to their P-stacking ability and specific H-bonding capacity [3]. High thermal stability of the compounds indicates their certain potential as monomeric building blocks in thin films and organometallic polymers [4]. Most of such pyridines demonstrate pronounced activity as antimalarial, vasodilator, anaesthetic, anticovulsant, antiepileptic, antitumor agents and some other biology and medicine related activities [5–7].

2,4,6-Triaryl substituted pyridines (Krohnke pyridines) [8] have been synthesized traditionally via the reaction of N-phenacyl pyridinium salts with α,β-unsaturated ketones in the presence of ammonium acetate [9]. Synthesis of poly substituted pyridines usually is carried out by multi component reactions that involve condensation of acetophenones and benzaldehydes with ammonia under high temperature and microwave irradiation [10]. Some recently developed methods involved microwave irradiation, ionic liquids, TMSI, I_2, NaOH in PEG-400 [11], PEG-300 along with NaOH [12], and catalytic amount of acetic acid [13].

RESULTS AND DISCUSSION

In the present study new 2,6-diphenyl-4-(1-phenyl-1*H*-1,2,3-triazol-4-yl)pyridines **(6a–6i)** were synthesized by the reaction of 1-Aryl-1*H*-[1,2,3]triazole-4-carbaldehyde (**4a–4c**) [14–16] with substituted acetophenones (**5a–5c**) and iodine/acetic acid by microwave irradiation with high yields. The newly synthesized compounds were characterized by IR, NMR and Mass spectral data.

Antibacterial activity. All synthesized compounds were screened *in vitro* for antibacterial activity against gram +ve bacterial strains Staphylococcus aureus (ATCC-9144), Bacillus cereus (ATCC-11778) and gram –ve bacterial strains Escherichia coli (ATCC-8739), Proteus vulgaris (ATCC-29213) by the cup-plate agar diffusion method at 25, 50 and 100 μg/mL concentrations. The zone of inhibition (in mm) was compared with the standard drug Ampicillin (Table 1). All synthesized compounds were active against the tested strains. The compounds **6e, 6f, 6i** demonstrated the highest potency.

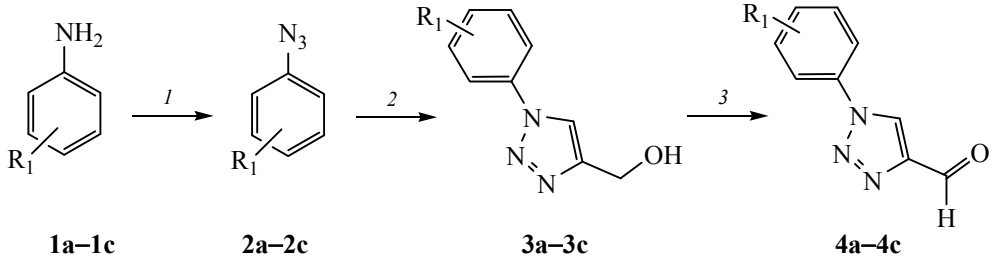
Antifungal activity. All synthesized compounds were screened *in vitro* for antifungal activity against Aspergillus Niger (ATCC-9029), Candida albicans (ATCC-2091), Aspergillus foetidus (NCIM-0505), and Candida rogosa (ATCC-9849). The zone of inhibition (in mm) was compared with standard drug Amphotericin-B (Table 2). The products demonstrated moderate to high activity against the tested fungal strains.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Gallen-Kamp MFB-595 apparatus. Elemental analysis was performed on a Perkin Elmer CHN-2400 analyzer. IR spectrum were recorded on a

[1] The text was submitted by the authors in English.

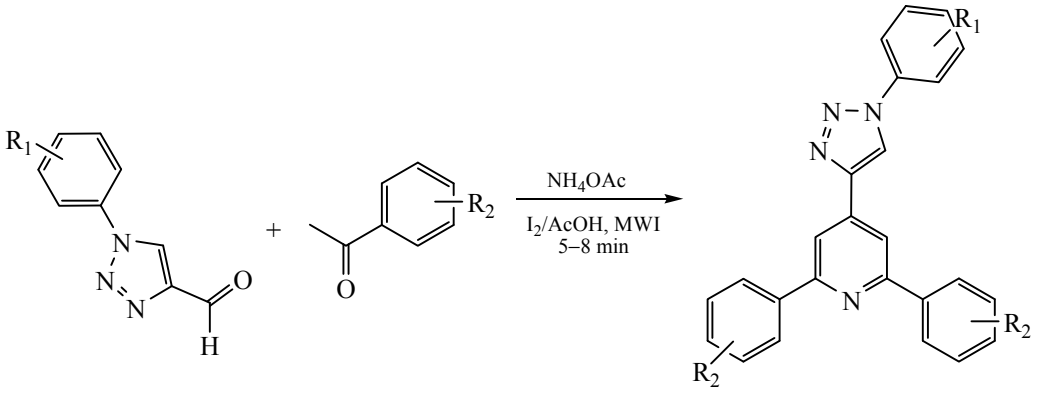
Scheme 1. Synthesis of 1-aryl-1*H*-[1,2,3]triazole-4-carbaldehydes (**4a-4c**).



1a–1c **2a–2c** **3a–3c** **4a–4c**

R_1 = H, 2-OMe, 2-Cl. (*1*) NaNO2, HCl 10%, 2–4 h, room temperature; (*2*) propargyl alcohol, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, H_2O : DMF (1 : 2), 3 h, room temperature; (*3*) IBX/DMSO, 3 h, room temperature.

Scheme 2. Synthesis of 2,6-diphenyl-4-(1-phenyl-1*H*-1,2,3-triazol-4-yl)pyridine (**6a-6i**).



4a–4c **5a–5c** **6a–6i**

R_1 = H, R_2 = H (**6a**); R_1 = H, R_2 = 4-Me (**6b**); R_1 = H, R_2 = 4-Cl (**6c**); R_1 = 2-Cl, R_2 = H (**6d**); R_1 = 2-Cl, R_2 = 4-Me (**6e**); R_1 = 2-Cl, R_2 = 4-Cl (**6f**); R_1 = 2-OMe, R_2 = H (**6g**); R_1 = 2-OMe, R_2 = 4-Me (**6h**); R_1 = 2-OMe, R_2 = 4-Cl (**6i**).

Perkin-Elmer FT-IR 8400s for KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 spectrometer in $CDCl_3$ using TMS as the internal standard. Mass spectra were recorded on a SHIMADZU LCMS 2020 mass spectrometers. Progress of reactions was monitored by TLC (Silica gel, aluminium sheets 60 F_{254}, Merck).

Synthesis of substituted 1-aryl-1*H*-[1,2,3]triazole-4-carbaldehydes 4a–4c. Mixture of a substituted 1-aryl-1*H*-[1,2,3]triazole-4-carbaldehyde (1 mmol), substituted acetophenone **5a–5c** (2 mmol), ammonium acetate (1.3 mmol) and I_2 (0.1 mmol) in acetic acid was treated by microwave irradiation. Progress of the reaction was monitored by TLC extracted with

Table 1. Antibacterial activity of compounds **6a–6i**

Product	Zone of inhibition, mm											
	S. aureus (ATCC-9144)			*B. cereus* (ATCC-11778)			*E. coli* (ATCC-8739)			*P. vulgaris* (ATCC- 29213)		
	25	50	100	25	50	100	25	50	100	25	50	100
6a	7	8	9	10	11	13	9	11	13	7	9	11
6b	6	7	9	8	9	12	9	11	13	8	10	12
6c	5	8	10	7	9	10	8	9	12	6	8	10
6d	6	7	10	8	10	12	9	11	12	7	9	11
6e	9	11	13	10	13	16	15	16	18	9	12	15
6f	10	12	13	12	15	18	15	17	19	12	14	18
6g	5	7	8	6	9	11	8	10	11	7	8	10
6h	6	7	9	7	9	11	10	11	12	7	8	11
6i	8	11	12	11	13	15	13	15	16	10	11	14
Ampicillin	8	10	11	10	13	16	13	15	17	10	12	15

Table 2. Antifungal activity of compounds **6a-6i**

Product	Zone of inhibition, mm											
	A.niger (ATCC-9021)			*A.foetidus* (NCIM-0505)			*C.albicans* (ATCC-2091)			*C.rogosa* (ATCC- 9849)		
	25	50	100	25	50	100	25	50	100	25	50	100
6a	6	8	9	6	7	9	5	7	9	5	6	7
6b	7	8	10	5	7	8	7	8	9	6	7	8
6c	5	8	9	7	9	10	6	7	8	6	7	7
6d	7	9	10	7	8	9	7	8	9	5	6	7
6e	11	12	14	10	11	12	9	11	12	9	10	12
6f	12	13	15	9	12	14	10	12	14	10	11	13
6g	5	7	7	6	6	8	7	8	9	6	7	8
6h	6	7	9	4	6	8	8	8	9	6	8	9
6i	9	11	12	8	10	12	9	10	11	7	8	11
Amphotericin B	10	12	13	9	11	13	10	11	12	8	9	11

ethyl acetate. The solvent was evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography using ethyl acetate–hexane (1 : 4) as an eluent to afford pure products.

2,6-Diphenyl-4-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-pyridine (6a). Yield 86%, mp 178–180°C. IR spectrum, ν, cm^{-1}: 1572, 1512. ^1H NMR spectrum, δ, ppm: 7.92 s (1H, triazole H), 7.62–7.74 m (7H, Ar-H), 7.58–7.64 m (10H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 150.1, 147.0, 131.2, 130.8, 130.5, 129.0, 128.6, 128.5, 127.2, 125.0, 123.1, 121.4, 120.0, 117.2, 115.9, 115.6, 110.7. *M* 375 $[M + H]^+$. Found, %: C 80.05; H 4.79; N 14.89. $C_{25}H_{18}N_4$. Calculated, %: C 80.19; H 4.85; N 14.96.

4-(1-Phenyl-1*H*-1,2,3-triazol-4-yl)-2,6-di-*p*-tolylpyridine (6b). Yield 85%, mp 190–192°C. IR spectrum, ν, cm^{-1}: 1576, 1520. ^1H NMR spectrum, δ, ppm: 8.01 s (1H, triazole H), 7.65–7.70 m (6H, Ar-H), 7.38–7.45 m (6H, Ar-H), 7.28–7.31 m (3H, Ar-H), 2.21 s (6H, Ar-CH_3). ^{13}C NMR spectrum, δ, ppm: 151.4, 147.8, 137.6, 131.3, 130.7, 129.3, 128.6, 127.1, 125.7, 125.0, 122.9, 122.7, 119.5, 117.2, 114.9, 114.8, 112.6, 20.3. *M* 403 $[M + H]^+$. Found, %: C, 80.48; H, 5.47; N, 13.87. $C_{27}H_{22}N_4$. Calculated, %: C, 80.57; H, 5.51; N, 13.92.

2,6-Bis(4-chlorophenyl)-4-(1-phenyl-1*H*-1,2,3-triazol-4-yl)pyridine (6c). Yield 90%, mp 196–198°C. IR spectrum, ν, cm^{-1}: 1579, 1523. ^1H NMR spectrum, δ, ppm: 7.9 m (3H, triazole H, Ar-H), 7.5 m (8H, Ar-H), 7.1 m (1H, Ar-H), 6.9 m (4H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 150.6, 147.6, 137.6, 131.1, 130.8, 129.3, 128.7, 127.1, 125.5, 125.0, 122.9, 122.2, 119.5, 117.5, 114.9, 114.6, 112.9. *M* 443 $[M + H]^+$. Found, %: C 67.65; H 3.62; N 12.58. $C_{25}H_{16}Cl_2N_4$. Calculated, %: C 67.73; H 3.64; N 12.64.

4-[1-(2-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-2,6-diphenylpyridine (6d). Yield 92%, mp 200–202°C. IR spectrum, ν, cm^{-1}: 1569, 1516. ^1H NMR spectrum, δ, ppm: 7.98 s (1H, triazole H), 7.79–7.83 m (3H, Ar-H), 7.65–7.69 m (3H, Ar-H), 7.32–7.38 m (10H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 149.5, 147.9, 134.9, 131.4, 130.6, 130.3, 129.1, 128.6, 127.7, 127.0, 124.9, 123.4, 123.2, 117.4, 115.3, 111.7. *M* 409 $[M + H]^+$. Found, %: C 73.40; H 4.11; N 13.66. $C_{25}H_{17}ClN_4$. Calculated, %: C 73.44; H 4.19; N 13.70.

4-[1-(2-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-2,6-di-*p*-tolylpyridine (6e). Yield 88%, mp 168–170°C. spectra, ν, cm^{-1}: 1581, 1516. ^1H NMR spectrum, δ, ppm: 7.95–7.98 m (3H, triazole H, Ar-H), 7.61–7.65 m (3H, Ar-H), 7.42–7.46 m (6H, Ar-H), 7.09–7.12 m (3H, Ar-H), 2.41 s (6H, Ar-CH_3). ^{13}C NMR spectrum, δ, ppm: 149.6, 147.8, 134.9, 130.6, 130.3, 129.2, 128.6, 127.7, 127.0 124.9, 123.6, 123.2, 117.3, 115.2, 112.8, 20.4. *M* 437 $[M + H]^+$. Found, %: C 74.14; H 4.78; N 12.75. $C_{27}H_{21}ClN_4$. Calculated, %: C 74.22; H 4.84; N 12.82.

2,6-Bis(4-chlorophenyl)-4-[1-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]pyridine (6f). Yield 90%, mp 160–162°C. IR spectrum, ν, cm^{-1}: 1575, 1518. ^1H NMR spectrum, δ, ppm: 8.01 s (1H, triazole H), 7.97–8.00 m (1H, Ar-H), 7.81–7.85 m (3H, Ar-H), 7.59–7.62 m (3H, Ar-H), 7.25–7.43 m (7H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 150.9, 147.9, 134.0, 131.4, 131.2, 129.7, 129.2, 128.6, 127.0, 124.9, 123.0, 121.4, 119.2, 117.3, 115.0, 112.8. *M* 477 $[M + H]^+$. Found, %: C 62.80; H 3.09; N 11.62. $C_{25}H_{15}Cl_3N_4$. Calculated, %: C 62.85; H 3.16; N 11.73.

4-[1-(2-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-2,6-diphenylpyridine (6g). Yield 90%, mp 195–197°C. IR spectrum, ν, cm^{-1}: 1577, 1515. ^1H NMR spectrum,

δ, ppm: 8.18 s (1H, triazole H), 7.94–7.98 m (2H, Ar-H), 7.42–7.55 m (8H, Ar-H), 7.20–7.26 m (6H, Ar-H), 3.81 s (3H, O-CH_3). ^{13}C NMR spectrum, δ, ppm: 150.9, 149.1, 147.0, 130.8, 130.5, 130.3, 129.0, 128.4, 127.1, 125.5, 123.8, 123.3, 120.8, 117.2, 115.8, 112.9, 110.8, 56.0. *M* 405 $[M + H]^+$. Found, %: C 77.12; H 4.82; N 13.78. $C_{26}H_{20}N_4O$. Calculated, %: C 77.21; H 4.98; N 13.85.

4-[1-(2-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-2,6-di-*p*-tolylpyridine (6h). Yield 86%, mp 188–190°C. IR spectrum, ν, cm^{-1}: 1580, 1518. ^{1}H NMR spectrum, δ, ppm: 8.52 s (1H, triazole H), 8.10–8.15 m (6H, Ar-H), 7.91–7.92 m (1H, Ar-H), 7.42–7.44 m (1H, Ar-H), 7.34–7.36 m (4H, Ar-H), 7.12–7.15 m (2H, Ar-H), 3.98 s (3H, O-CH_3), 2.23 s (3H, Ar-CH_3). ^{13}C NMR spectrum, δ, 157.5, 151.5, 145.5, 139.4, 139.0, 136.7, 130.4, 129.3, 127.0, 126.1, 125.5, 123.2, 121.3, 114.6, 112.3, 56.1, 21.3; *M* 433 $[M + H]^+$. Found, %: C 77.62; H 5.45; N 12.90. $C_{28}H_{24}N_4O$. Calculated, %: C 77.75; H 5.59; N 12.95.

2,6-Bis(4-chlorophenyl)-4-(1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)pyridine (6i). Yield 92%, mp 164–167°C. IR spectrum, ν, cm^{-1}: 1578, 1522. ^{1}H NMR spectrum, δ, ppm: 8.39 s (1H, triazole H), 7.96–8.02 m (4H, Ar-H), 7.95–7.98 m (3H, Ar-H), 7.62–7.66 d (3H, *J* =15.1 Hz, Ar-H), 7.41–7.45 m (1H, Ar-H), 7.18–7.20 m (3H, Ar-H), 3.95 s (3H, O-CH_3). ^{13}C NMR spectrum, δ, ppm: 150.9, 147.0, 130.8, 130.6, 130.3, 129.0, 128.5, 127.1, 125.4, 124.9, 123.7, 123.0, 120.8, 117.2, 116.2, 112.9, 112.8, 110.8, 56.3. *M* 473 $[M + H]^+$. Found, %: C 65.91; H 3.76; N 11.78. $C_{26}H_{18}Cl_2N_4O$. Calculated, %: C 65.97; H 3.83; N 11.84.

CONCLUSIONS

In the present study a number of new 2,6-diphenyl-4-(1-phenyl-1*H*-1,2,3-triazol-4-yl)pyridines (**6a-6i**) has been synthesized via the three-component one-pot reaction of substituted 1-phenyl-1*H*-[1,2,3]triazole-4-carbaldehydes with substituted acetophenones and ammonium acetate. All synthesized compounds have been characterised by spectral data and elemental analysis. All compounds demonstrated high antimicrobial activity against bacteria and fungi.

ACKNOWLEDGMENTS

Authors are grateful to the Head, Department of Chemistry, Osmania University for providing laboratory facilities, and Director, Central Facilities for Research and Development (CFRD), Osmania University, Hyderabad for providing spectral data. One of the authors BR is grateful to UGC, New Delhi for award of SRF. Another author (NJPS) is also thankful to UGC (MRP-F no. 39-772/2010(SR) and OU-DST-PURSE Programme (no. A-37/PURSE/coord/2012 for financial support.

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