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SYNTHESIS AND MICROBIAL EVALUATION OF NOVEL TETRAZOLO-TRIAZOLE DERIVATIVES

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Abstract:
5-(4'-Bromomethyl-1, 1'-biphenyl-2-yl) -1H-tetrazole **(1)** was converted into its azide derivative using sodium azide **(2)**, which on further treatment with malonitrile, diethyl malonate, ethyl acetoacetate and isopropyl acetoacetate to yielded the respective tetrazole-triazole derivatives. The structures of the synthesized compounds were confirmed by Physico-chemical test and spectral techniques, representative samples were screened for their antimicrobial activity against gram positive and gram negative bacteria.
Key words: Tetrazoles, Triazoles, Triphenyl phosphine, azides.

Introduction:

Azides are considered to be very important compounds due to both their industrial as well as biological applications [I]. Azide derivatives have been used in rubber vulcanization, polymer crosslinking, dyes, tire cored adhesives, foaming of plastics, pharmaceuticals, pesticides and herbicides [I]. Many azide compounds show mutagenic activities [II-IV].
The chemistry of azides has thus attracted the attention of many chemists, since many of these compounds played an important role in organic chemistry [V-VII]. One of the more useful synthetic applications of azides is the preparation of 1,2,3-triazoles via 1,3-dipolar cycloaddition reactions of azides with substituted acetylene compounds [VIII-XIII]
The chemistry of 1,2,3-triazoles has also received much attention because of their wide range of applications. They have been used as fungicides, herbicides, light stabilizers, fluorescent whiteners, optical brightening agents, and corrosion retardants [XIV-XVI]. Moreover 1,2,3-triazole derivatives shows significant antimicrobial, cytostatic, virostatic and anti-inflamatory activities[XVII].

Experimental

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as

visualizing agent. ^{1}H NMR spectra were recorded on Varian 300 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

Synthesis of 5-(4'-Bromomethyl-1, 1'-biphenyl-2-yl)-1H-tetrazole (1) :
To precool (5-10°C) mixture of water and sodium azide (1 mol) triphenyl phosphine chloride (1 mol) was added lot wise. The resulting mixture was stirred for 1 hr. the complex thus formed was extracted with dichloromethane (MDC). The organic layer was washed with water, dried over sodium sulphate and was added to 2-cyano-4'-bromomethyl-biphenyl (1 mol) in o-Xylene. The contents were refluxed for 6-7 hrs. The progress of the reaction was monitored on TLC. Upon completion, reaction mass quenched onto cold water, separated the organic layer. Organic layer washed with water, dried over sodium sulphate and distilled under vacuum to yield the white crystals of **(1).**
m.p. = 155-57°C, yield = 87 %

Synthesis of 5-(4'-azido-methyl-1, 1'-biphenyl-2-yl)-1H-tetrazole (2)
A suspension of **(1)** (0.01 mol) and sodium azide (0.015 mol) in dry dimethylformamide (30ml) was stirred at 20°C for 4-5 hours. The progress of the reaction was monitored by TLC. Upon Completion, the reaction mixture was poured into ice-cold water (500ml). The product thus obtained, was filtered, washed with cold water, followed by ether to get **(2).**
m.p. = >240°C, yield = 92 %

Synthesis of (3)-(6) (General Procedure)
A mixture of active Methylene compound (0.1 mol) (diethyl malonate, malonitrile, ethylacetoacetate and isopropyl acetoacetate) in ethanol and Sodium ethoxide (0.25 mol) was cooled to 0-5°C. The content was stirred for 30 mins. A solution of **(2)** (0.1 mol) in ethanol was added dropwise, while maintaining the temp 0-5°C. Reaction mixture was stirred at R.T. for 10-12 hr. The progress of the reaction was monitored by TLC. Upon Completion of the reaction, mixture was concentrated under vacuum and poured into ice-cold water. The product was extracted by ethyl acetate. On evaporation under reduced pressure the crude product further purified by column chromatography using n-Hexane and Ethyl acetate (70:30) to yield the desired product **(3-6).**

Spectral Interpretation:
5(4″H-4″-carbethoxy-1″,2″,3″-triazole-5″-one-1″-yl-methyl-1,1′biphenyl2-yl)-1H-tetrazole, (3)
Yield: 72%; m.p. =141-145°C: IR (cm-1): 1735 (C=O), 1700 (C=N), 1685(C=O), ^{1}H NMR (DMSO-d6, δ/ ppm): 1.31 (t, 3H, CH_3), 3.10 (s, 1H, CH), 4.12 (q, 2H, OCH_2), 4.48 (s, 2H, Ar-CH_2), 7.10-7.60 (m, 8H, Ar -H), 9.0 (s, 1H, NH), ^{13}C NMR (DMSO-d6, δ/ ppm): 15.24 (CH_3), 45.59 (CH_2), 59.14 (CH), 60.21 (CH_2), 120.48- 132.48 (Ar-C), 155.42 (C=N), 158.53 (C=N), 178.41 (C=O), 179.29 (C=O). LCMS; m/z: 391; Anal.Calcd for $C_{19}H_{17}N_7O_2$: C, 58.21; H, 4.31; N, 25.40% Found: C, 58.22; H, 4.18, N, 25.35 %.

5(4″-carbethoxy-5-methyl-1″,2″,3″-triazole-5″-one-1″-yl-methyl-1,1′biphenyl2-yl)-1H-tetrazole (4)
Yield: 80%; m.p. =122-24°C: IR (cm-1): 1745 (C=O), 1690 (C=N), ^{1}H NMR (DMSO-d6, δ/ ppm): 1.35 (t, 3H, CH3), 2.20 (s, 3H CH_3), 4.20 (q, 2H, OCH_2), 4.50 (s, 2H, Ar-CH_2), 7.15-7.70 (m, 8H, Ar -H), 8.8.0 (s, 1H, NH), ^{13}C NMR (DMSO-d6, δ/ ppm): 9.14 (CH_3), 16.48 (CH_3), 46.74 (CH_2), 60.21 (CH_2), 122.67- 134.21 (Ar-C), 156.34 (C=N), 179.18 (C=O).
LCMS; m/z: 389; Anal.Calcd for $C_{20}H_{19}N_7O_2$: C, 61.69; H, 4.92; N, 25.18%. Found:
C, 61.22; H, 4.80, N, 24.95 %.

5(4″-carbethoxy-4-cyno-5-amino-1″,2″,3″-triazole-5″-one-1″-yl-methyl-1,1′biphenyl2-yl)-1H-tetrazole (5)
Yield: 70%; m.p. =125°C: IR (cm-1): 2250 (CN), 1685 (C=N), 1H NMR (DMSO-d6, δ/ ppm): 4.00 (s, 2H, NH_2), 4.50 (s, 2H, Ar-CH_2), 7.09-7.50 (m, 8H, Ar -H), 8.40 (s, 1H, NH), ^{13}C NMR (DMSO-d6, δ/ ppm): 44.28 (CH_2), 117.24 (CN), 121.47- 130.24 (Ar-C), 156.34 (C=N), LCMS; m/z: 343; Anal.Calcd for $C_{17}H_{13}N_9$: C, 59.47; H, 3.82; N, 36.72%. Found:
C, 60.22; H, 3.70, N, 36.95 %.

5(4″H-4″-isopropyl-1″,2″,3″-triazole-5″-one-1″-yl-methyl-1,1′biphenyl2-yl)-1H-tetrazole (5)
Yield: 65%; m.p. =106°C: IR (cm-1):1720(C=O), 1671 (C=N), ^{1}H NMR (DMSO-d6, δ/ ppm): 1.35 (d, 6H, CH3), 1.55 (m, 1H, CH3), 2.92 (d, 1H, CH), 4.50 (s, 2H, Ar-CH_2), 7.15-7.70 (m, 8H, Ar -H), 8.8.0 (s, 1H, NH), ^{13}C NMR (DMSO-d6, δ/ ppm): 18.24 (2x CH_3), 39.84 (CH), 46.18 (CH_2), 60.27 (CH), 119.77- 128.31 (Ar-C), 158.17 (C=N),178.54 (C=O).
LCMS; m/z: 361; Anal.Calcd for C19H19N7O: C, 63.14; H, 5.30; N, 27.13. Found:
C, 63.22; H, 5.20, N, 26.95 %.

Antimicrobial and antifungal activities
All the newly synthesized compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method [XVIII-XIX]. The zone of inhibition was measured in mm and the activity was compared with standard drug. The data is given in **TABLE I**.

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General Scheme

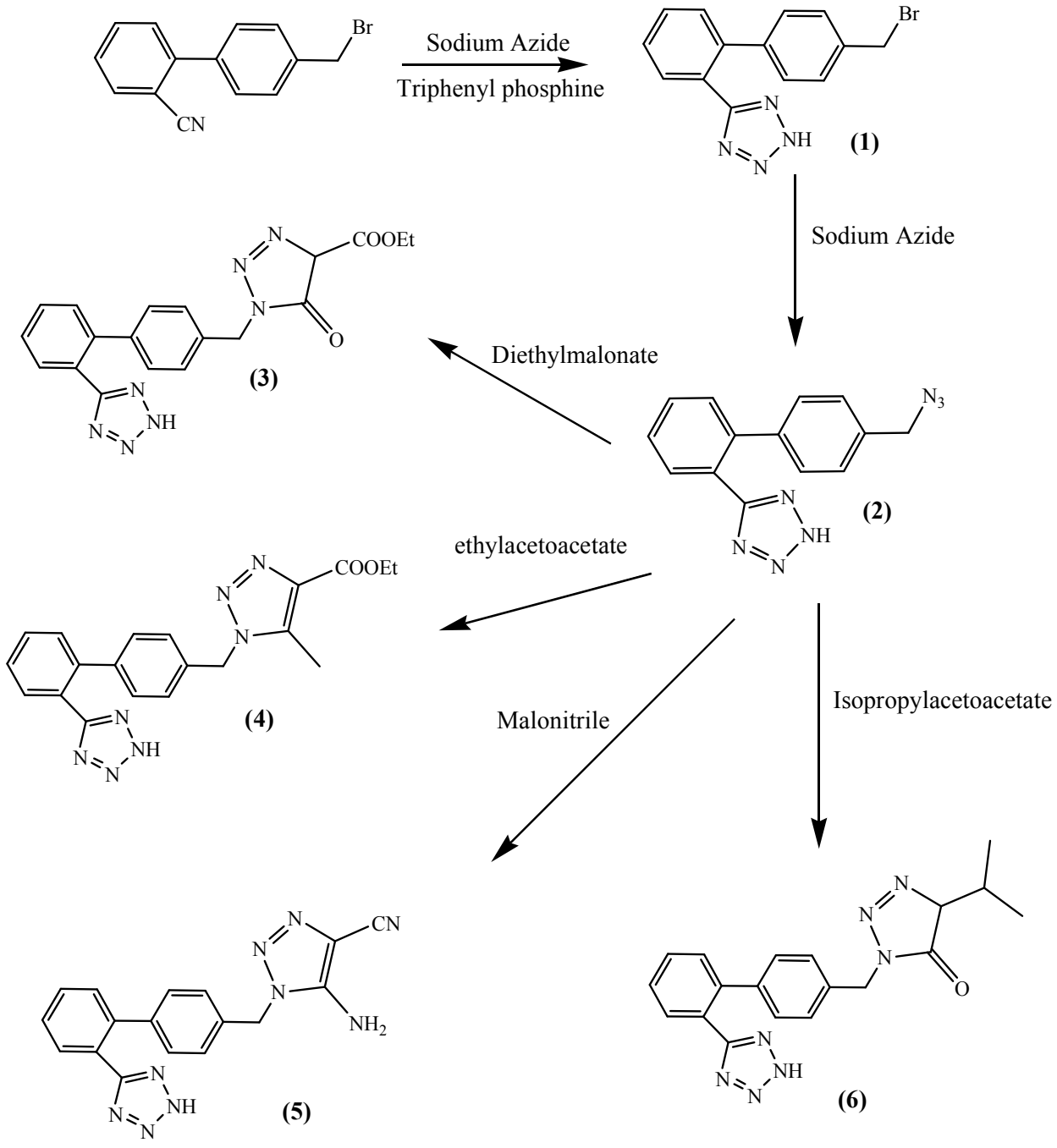

Table I. **Antimicrobial activities of some newly synthesized compounds.**

Compds	Inhibition Zone (mm)						
	Gram-negative		Gram-positive		Fungi		Yeast
	E.coli	*P.Putide*	*B.Subtilis*	*S.lactis*	*A.niger*	*P.Sp.*	*C.Albicans*
3	17	15	18	21	17	10	8
4	16	16	17	21	19	10	9
5	15	14	18	19	18	11	9
6	18	19	19	20	18	12	10
DMSO	0	0	0	0	0	0	0
Ampicilin ®	24	20	19	22	24	14	14

E.coli. = Escherichia coli; P.Putide = Pseudomonas Putide; B. Subtilis = Bacillus Subtilis; S. lactis = Sterptococcus lactis; A. niger = Aspergillus niger; P. Sp. = Penicillium Sp; C. Albicans = candida Albicans.

The sensitivity of microorganisms to the tested compounds is identified in the following manner*;

Highly Sensitive = Inhibition zone: 15-20 mm

Moderately Sensitive = Inhibition zone: 10-15 mm

Slightly Sensitive = Inhibition zone: 5-10 mm

Not Sensitive = Inhibition zone: 0 mm

* Each result represents the average of triplicate readings.