Nanomed Res J 4(2):91-100, Spring 2019

RESEARCH ARTICLE

Synthesis of 1,5 and 2,5-disubstituted tetrazoles and their evaluation as antimicrobial agents

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ARTICLE INFO

Article History:
Received 14 March 2019
Accepted 27 May 2019
Published 15 June 2019

Keywords:
2,5-Disubstituted Tetrazoles
Antimicrobial
NiO Nanoparticles
Tetrazolate Salts

ABSTRACT

Treatments of tetrazolate salts, malononitrile and sodium azide using NiO nanoparticles with benzyl bromide gave the corresponding 1,5- and 2,5-disubstituted tetrazoles. Reaction of tetrazolate salts with 2,4′-dibromoacetophenone by NiO nanoparticles provided 2,5-disubstituted derivatives as an only isomer. The structures of tetrazoles were characterized by ^{1}H and ^{13}C NMR spectra, FT-IR spectra, MS and elemental analysis. Use of simple and readily accessible starting materials, excellent yields, reusability of the catalyst, short reaction times, low amount of catalyst are some advantages of this protocol. Their antimicrobial activity has been tested *in vitro* against Gram positive bacteria; Gram negative bacteria and fungi. Four compounds have only moderate growth inhibitory effects against Gram positive bacteria. The antimicrobial screening suggests that compounds **5h**; **6h**; **5g** and **6g** have only medium growth inhibitory effects against Gram positive bacteria. Among the newly synthesized compounds; good antimicrobial activity was observed for compound **6g** against *Staphylococcus epidermidis* (MIC value 125 μg/ml).

How to cite this article
Safaei-Ghomi J, Paymard-Samani S, Zahraie Z, Shahbazi-Alavi H. Synthesis of 1,5 and 2,5-disubstituted tetrazoles and their evaluation as antimicrobial agents. Nanomed Res J, 2019; 4(2): 91-100. DOI: 10.22034/nmrj.2019.02.006

INTRODUCTION

The family of tetrazoles is known as a highly main moiety in organic; organometallic; medicinal chemistry [1-6], and in diverse materials science including propellants [7], and inflammables [8], 1,5- and 2,5-disubstituted tetrazoles are also significant as NAD(P)H oxidase inhibitors [9], potential TNF-α inhibitors [10], hepatitis C virus (HCV) serine protease NS3 inhibitors [11], selective cyclooxygenase-2 (COX-2) inhibitors [12], calcitonin gene-related peptide receptor antagonists, antimigraine [13], antiviral and antiproliferative activity [14, 15]. Several procedures have been developed in literature for the preparation of tetrazoles [16,17]. To prepare these compounds, the alkylation of tetrazole anions are utilized. However; owing to the ambient nature of the anions **1a**↔**1b**, the metal salt products of 5-substituted tetrazoles undergo to alkylation with electrophiles in a vast range of solvents afforded mixture of 5-substituted 1N- and 2N-alkyl tetrazoles (Scheme 1) [18]. For instance; the reaction of 5-substituted tetrazoles with epoxy compounds [19] dialkyl sulfates [20], benzyl bromide [21], and alkyl halides [22], using base; or with diazomethane, [23] afford a mixture of 1,5 and 2,5-disubstituted tetrazoles and the ratio of the regioisomers are affected by the electronegativity and size of the 5-substituent. Even by obstructing the *N*(2)-position with tri-*n*-butyltin before alkylation; the 2,5-isomer was formed about a 10% yield [24].

Nelson et al prepared a series of complexes including of the 1,5- disubstituted tetrazoles individually by obstructing the 2-position with cobalt complexes [25]. Kondo et al obtained 2,5-diarylsubstituted tetrazoles from phenyl sulfonyl hydrazones of aromatic aldehydes and arenediazonium salts [26]. Yamamoto and co-workers were prepared 2,5-disubstituted tetrazoles

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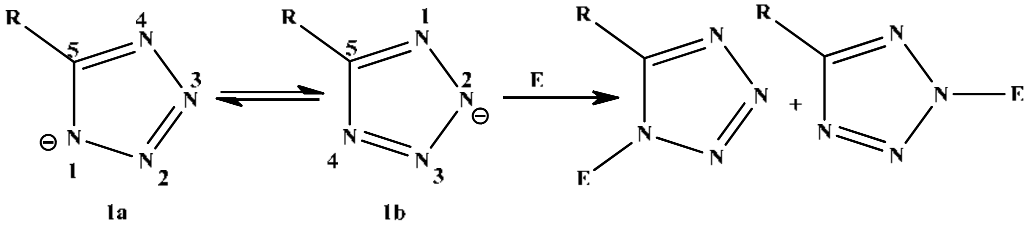
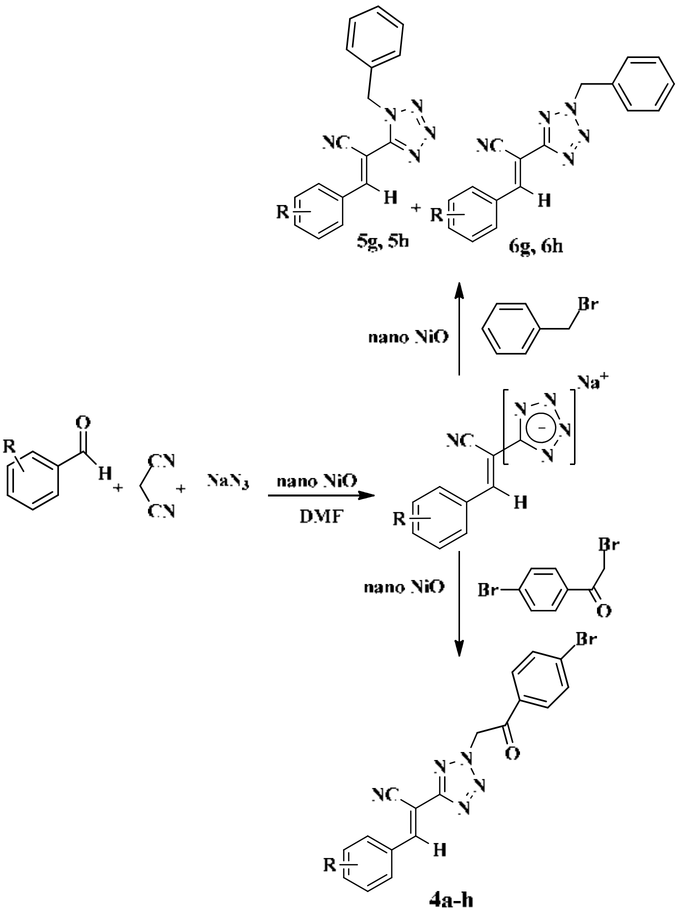


Scheme 1. Alkylation of tetrazolate anion to produce a mixture of 1,5- and 2,5-disubstitted tetrazoles



Scheme 2. Preparation of 1,5 and 2,5-disubstituted tetrazoles

by palladium-catalyzed reaction of nitriles; trimethyl-silylazide, and allyl acetates [27].

Multi-component reactions (MCRs) are efficient and rapid methods for the preparation of single reactive intermediate or products from several starting materials [28,29]. Transition metal-catalyzed multi-component systems have recently increased substantial interest [30,31]. Lately, nickel-based nanoparticles and especially NiO nanoparticles have been utilizeed as effective heterogeneous catalysts for organic reactions [32-35]. Our interest on the preparation of heterocyclic compounds and the development of efficient methods for MCRs which were catalyzed by nanoparticles [36-38], led us to the generation of regioselected 2,5-disubstituted tetrazoles **4a-h** by Knoevenagel condensation/1,3-dipolar cycloaddition reaction of aldehydes, sodium azide, malononitrile, and 2,4′-dibromoacetophenone using nano-NiO as a catalyst.

The catalyst were prepared according to the procedure presented by Zhang et al from the reaction of NaCl and $Ni(OH)_2$ [39-41].

Recently we reported an efficient method for the synthesis of 2-(1H-tetrazol-5-yl) acrylonitrile derivatives (3) starting from aldehydes (1); malononitrile (2) and sodium azide continued by acidic hydrolysis [35]. The best result was achieved at 70°C with 6 mol % nanocrystalline in DMF.

We continued working to expand the groups of tetrazole heterocyclic compounds by beginning from this effective reagent. The first outcome of this project is the preparation of 1,5-disubstituted and 2,5-disubstituted tetrazoles from benzyl bromide and tetrazolate salts by an expeditious approach. Then we obtained the regioselected compounds of a series of new 2,5-disubstituted tetrazoles through treatment of tetrazolate salts with 2,4′-dibromoacetophenone (Scheme 2). The antimicrobial screening results against Gram negative bacteria; Gram positive bacteria and fungi are presented for compounds **4a**, **4b**, **4f**, **5g**, **5h**, **6g** and **6h**.

EXPERIMENTAL SECTION

General procedure for the preparation of disubstituted tetrazoles

Nano NiO (6 mol %) is added to a mixture of aromatic aldehyde (1.0 mmol); malononitrile (1.0 mmol) and NaN_3 (1.0 mmol) in DMF (5 mL) and stirred at 70 °C. Then, the mixture was cooled to room temperature. Afterwards, benzyl bromide (1.0 mmol) or 2,4′-dibromoacetophenone (1.0 mmol) was added. The contents were further stirred at 70 °C until completion (monitoring by TLC). After completion; the nanocatalyst was separated off by centrifugation and rinsed with acetone (3 times). Water was added to precipitate. The precipitate was filtered and dried. Most of the compounds were obtained in pure form after easy trituration with ethyl acetate and hexane. Other compounds were purified by column chromatography ($CHCl_3$/CH_3OH 9.5:0.5). In a representative case (Entry 1; Table 1); the recovered catalyst was reused in three successive runs without any considerable reduce in the product yields.

Determination of Antimicrobial activity

Microbial strains

Products of **4a**, **4b**, **4f**, **5g**, **5h**, **6g** and **6h** were appraised *in vitro* against for antibacterial activities against *Pseudomonas aeruginosa* (ATCC 27853); *Escherichia Coli* (ATCC 10536); *Klebsiella pneumonia* (ATCC 10031); *Shigella dysenteriae* (PTCC 1188); *Proteus vulgaris* (PTCC 1182) and *Salmonella paratyphi-A serotype* (ATCC 5702) as examples of Gram negative bacteria; *Bacillus subtilis* (ATCC 6633); *Staphylococcus aureus* (ATCC 29737) and *Staphylococcus epidermidis* (ATCC 12228) as examples of Gram positive bacteria. They were appraised in vitro for their antifungal activities against *Candida albicans* (ATCC 10231); *Aspergillus niger* (ATCC 16404) and *Aspergillus brasiliensis* (ATCC 16404) as examples of fungal strains.

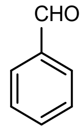
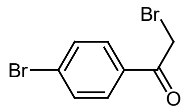
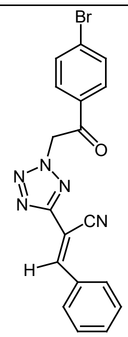
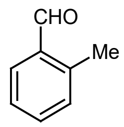
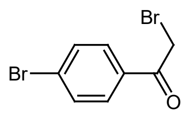
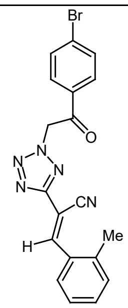
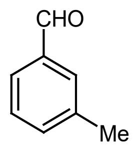
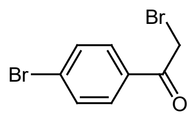
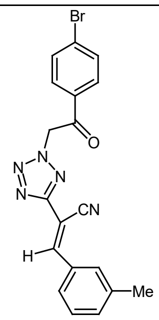
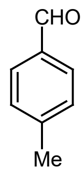
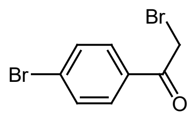
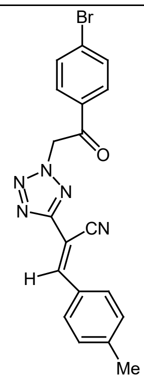
Agar diffusion assay

Agar diffusion technique was utilized for determining preparatory antibacterial and antifungal activities [43]. Each of the test compounds was dissolved in DMSO as solvent to final concentration of 30 mg/ml and filtered by 0.45 μm Millipore filters for sterilization. One-hundred microliters of suspension including 10^8 CFU/ml of bacteria; 10^6 CFU/ml of yeast and 10^4 spore/ml of fungi spread on the nutritious agar; sabouraud dextrose agar and potato dextrose agar medium; respectively. Uniform wells (6 diameters) were punched on the media plates and filled with 10 μl of the test compounds. Streptomycin (10μg/well) was utilized as positive control for bacteria and Nystatine (100 IU/well) for fungi. DMSO was applied as a negative control. The inseminated plates were incubated for at 37°C for 24 h bacterial strains and 48 h and 72 h at 30°C for yeast and mold isolated; respectively. The results were noted for each tested compound as average diameter of inhibition zones of bacterial and fungal around the wells in mm and each test was repeated twice.

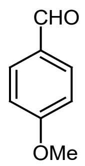
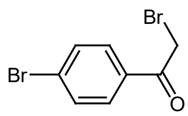
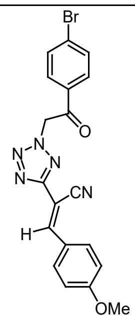
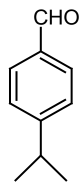
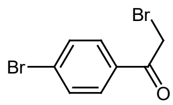
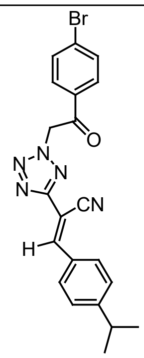
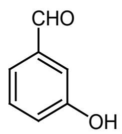
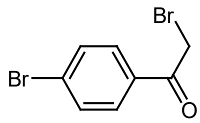
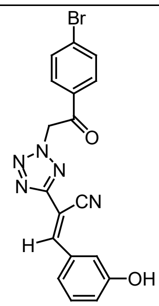
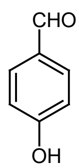
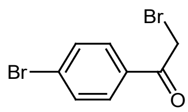
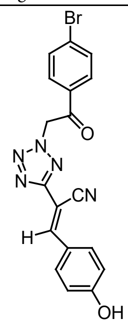
Micro-well dilution assay

Bacterial strains sensitive to the compounds in agar diffusion assay were investigated for their minimum inhibitory concentration (MIC) values using micro-well dilution assay procedure [44]. The inocula of microbial strains were provided from 12 h broth cultures and suspensions were modified to 0.5 McFarland standard turbidity. The compounds were dissolved in 10% DMSO as solvent and diluted to the highest concentration (2000 μg/ml) to be tested and then serial twofold dilutions were prepared in a concentration range from 31.25 to 2000 μg/ml in 10 ml sterile tubes including brain heart infusion (BHI) broth. The 96-well plates were provided by dispensing 95 μl of the cultures media and 5 μl of the inoculums into

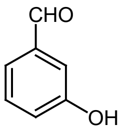
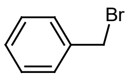
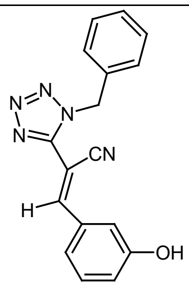
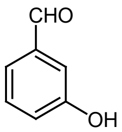
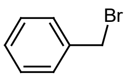
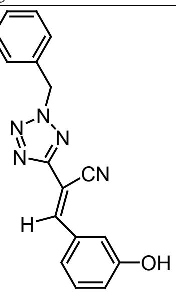
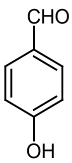
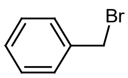
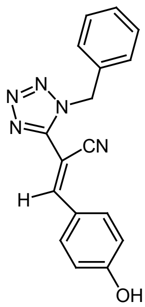
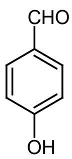
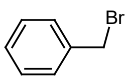
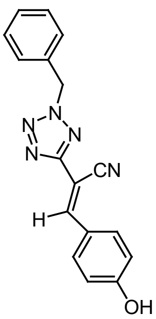
Table 1. Synthesis of disubstituted tetrazoles catalyzed by NiO NPs (6 mol%) at 70°C in DMF

Entry	R	R-Br	Product	Time (min)	Mp (°C)	Yield%[a]
1			 4a	120	188-190	90 89[b] 89[c]
2			 4b	120	173-174	85
3			 4c	123	189-190	88
4			 4d	120	216-218	87

Continued Table 1. Synthesis of disubstituted tetrazoles catalyzed by NiO NPs (6 mol%) at 70°C in DMF

Entry	R	R-Br	Product	Time (min)	Mp (°C)	Yield%[a]
5			 4e	120	202-203	85
6			 4f	127	177-179	84
7			 4g	120	201-202	86
8			 4h	124	249-251	85

Continued Table 1. Synthesis of disubstituted tetrazoles catalyzed by NiO NPs (6 mol%) at 70°C in DMF

Entry	R	R-Br	Product	Time (min)	Mp (°C)	Yield%[a]
9			 5g	212	236-238	86[d]
10			 6g	212	149-151	
11			 5h	260	230-231	85[e]
12			 6h	260	162-163	

[a]Yield of isolated product
[b,c]These yields correspond to the second and third runs; respectively; with the recycled catalyst.
[d]Yield of mixture products (5g and 6g)
[e]Yield of mixture products (5hand 6h)

each well. A 100 µl aliquot from the stock solutions of the compounds was made at the concentration of 2000 µg/ml was added into the first well. Then 100 µl from their serial dilutions was transferred into six successive wells. The last well comprising 195 µl of the cultures media without the test materials and 5 µl of the inoculums on each strip was applied as the negative control. Streptomycin was utilized as standard drug for positive control in conditions similar to tests materials. Turbidity indicated growth of microorganism and the MIC were determined as the lowest concentrations of the compounds that prevented visible growth.

RESULTS AND DISCUSSION

Chemistry

The morphology of nano-NiO was determined by Scanning Electronic Microscopy (SEM). The results from SEM images clearly demonstrate that the average size of nano-NiO is about nanometers (Fig. 1).

Fig. 1

It has been reported formerly that the reaction of tetrazolate salts with halogenoalkanes gave the 1,5-disubstituted and 2,5-disubstituted tetrazoles as mixtures [21,22]. Treatment of tetrazolate salts prepared *in situ* with benzyl bromide offered the corresponding mixtures of 1,5-disubstituted **5** (minor isomers) and 2,5- disubstituted **6** (major isomers) derivatives (Table 1; entry 9, 10). TLC of this solution indicated them to be a mixture of two products; which was separated by silica gel column chromatography using $CHCl_3/CH_3OH$ as eluent. In their mass spectra; both of these compounds; the low (**5g, 5h**) and the high (**6g, 6h**) moving; showed the same molecular ion peak illustrated them to be the positional isomers. In the ^{13}C NMR spectra the carbon CH_2 attached to tetrazole are very obvious, appearingat *ca*. 51.6 ppm in isomers **5h** and at *ca*. 56.8 ppm in isomers **6h**, also vinylic carbon attached to nitrile group (88.87 ppm for isomer **5h** and 93.35 ppm for isomer **6h**. In ^{1}H NMR spectra of (*E*)-2-(2-benzyl- 2*H*-tetrazol-5-yl)-3-(4-hydroxyphenyl) acrylonitrile (**6h**) the appearance of resonance signal for CH_2 attached to tetrazole ring at 5.96 is relatively at higher field than the resonance signals at 5.85 for CH_2 attached to tetrazole ring in (*E*)-2-(1-benzyl-1 *H*-tetrazol-5-yl)-3- (4- hydroxy phenyl) acrylonitrile (**5h**) further supporting their assigned structures. The ratio of isolated yields of the above two isomers (ratio of **6g/5g** is 8.6 and ratio of **6h/5h** is10.8) determined by ^{1}H NMR. These results suggested that the **6g;h** isomers are the predominant ones (Table 1). Steric factors also have a vital role in the ratio for formation of isomers [40-42].

Treatment of tetrazolate salts with 2,4′-dibromoacetophenone gave the corresponding 2,5-disubstituted derivative as an only isomer. TLC of the reaction mixture showed the product to be one isomer. The best evidences for the formation of 2,5-disubstituted derivative are its less steric hindrance which is explained in suggested mechanism and the appearance of a deshielded singlet for CH_2 attached to tetrazole ring (6-7 ppm) in the ^{1}H NMR spectrums of **4a**-**4h**.

Antimicrobial activity

The results of antimicrobial activity of compounds are presented in Table 2 and 3. Our

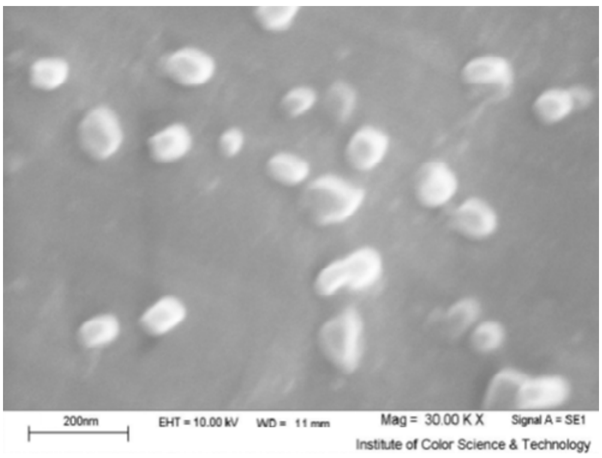


Fig. 1. SEM image of NiO nanoparticles

Table 2. *In vitro* antimicrobial activity of the prepared compounds by agar diffusion assay.

Test microorganisms	Diameter of zone of inhibition in mm								
	4a	4d	4f	5h	6h	5g	6g	Streptomycin	Nystatin
P. aeruginosa	*	*	*	*	*	*	*	22	NT
E. coli	*	*	*	*	*	*	*	25	NT
K. pneumonia	*	*	*	*	*	*	*	24	NT
S. dysenteriae	*	*	*	*	*	*	*	24	NT
P. vulgaris	*	*	*	*	*	*	*	23	NT
S. paratyphi-A	*	*	*	*	*	*	*	28	NT
B. subtilis	*	*	*	10	13	10	10	25	NT
S. aureus	*	*	*	10	11	11	13	28	NT
S. epidermidis	*	*	*	11	10	12	13	22	NT
C. albicans	*	*	*	*	*	*	*	NT	25
A. niger	*	*	*	*	*	*	*	NT	32
A. brasiliensis	*	*	*	*	*	*	*	NT	33

*Not Active.
NT: not tested.

Table 3. Minimum inhibitory concentration (MIC in μg/ml) values of the effective prepared compounds.

Microorganisms	Products			
	6h	5h	6g	5g
B. subtilis	2000	2000	1000	1000
S. aureus	2000	2000	2000	2000
S. epidermidis	250	250	125	500

results demonstrated that the synthetic compounds **4a**, **4b**, **4f**, **5g**, **5h**, **6g** and **6h** have no antimicrobial effect against Gram negative bacteria and fungi. The compounds **5h**; **6h**; **5g** and **6g** have only moderate growth inhibitory effects against Gram positive bacteria (*Bacillus subtilis*; *Staphylococcus aureus* and *Staphylococcus epidermidis*) (Table 2).

As displayed in Table 3; the results of the MIC values of the elected compounds in all cases were more than 500 μg/ml against *Bacillus subtilis* and *Staphylococcus aureus*. Compound **5h** and **6h** showed MIC values 250 μg/ml against *Staphylococcus epidermidis* and good antimicrobial activity was apperceived for compound 6g against *Staphylococcus epidermidis* (MIC value 125 μg/ml).

CONCLUSIONS

In conclusion, we have improved an efficient procedure for the preparation of disubstituted tetrazoles in the present of NiO nanoparticles. Reaction of tetrazolate salts and 2,4′-dibromoacetophenone in the presence of NiO NPs provided the regioselected products. This procedure offers several advantages; containing facile; excellent yields in short time; ease of experimental method; and environmentally friendly. The antimicrobial screening suggests that compounds **5h**; **6h**; **5g** and **6g** have only medium growth inhibitory effects against Gram positive bacteria. Among the newly synthesized compounds; good antimicrobial activity was observed for compound **6g** against *Staphylococcus epidermidis* (MIC value 125 μg/ml).

Supporting Information

Experimental method and product characterization data: IR, ^{1}H NMR, ^{13}C NMR and elemental analyses of the selected compounds are presented in Supporting Information.

ACKNOWLEDGEMENT

The authors are grateful to university of Kashan for supporting this work.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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