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# A ONE POT METHOD FOR THE SYNTHESIS OF 1-(2-TRIFLUOROMETHANPHENYL)-5-PHENYL-1H-TETRAZOLE (1, 5-DISUBSTITUTED TETRAZOLE) CATALYZED BY ZIRCONIUM OXYCHLORIDE AND THEIR ANTIBIOTIC ACTIVITY

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**ABSTRACT:**
Synthesis and antibiotic activity of 1, 5-disubstituted tetrazole in 88% yield using zirconium oxychloride in the presence of sodium azide and acetonitrile as solvent with zirconium oxychloride, Sodium azide was used as an azide transfer reagent as it transformed the amide to an imidoyl azide intermediate and, then, by ring closing, to tetrazole. The formation of hindered 1, 5-disubstituted tetrazole was confirmed by $^{1}$H-, $^{13}$C-, and $^{19}$F-NMR, HRMS, and FT-IR. Synthesized compound were screened for their in vitro antibacterial activities against B.subtilis, B.sphaericus, S.aureus, P.aeruginosa, K.aerogenes, C.violaceum.

**KEYWORDS:** 1,5-Disubstituted tetrazole, Zirconium Oxychloride and Sodium Azide, Bulky secondary N-benzoyl amide, imidoylazides.

## INTRODUCTION:

Tetrazoles are crucial in pharmacological and medical research. Tetrazole chemicals as a class have recently been employed as both anticancer and antibacterial agents [i]. Due of their potential biological activity and industrial applications, they have drawn more attention [ii]. Additionally, the carboxy group and amide bond in the molecules of peptidomimetics can be replaced by tetrazole fragment, which is metabolically stable [iii]. McManus and Herbst provided the first description of amino acid derivatives with a 5-tetrazolyl substituent [iv]. Later, Zabrocki et al. suggested using the 1,5-diyl fragment of tetrazole to synthesize peptidomimetics having cis-block peptide bonds [v]. Numerous studies have been conducted in an effort to create efficient procedures for the creation of amide derivatives having a tetrazoles moiety in response to the growing demand for the synthesis of tetrazoles containing peptides and peptidomimetics.

The 1,5-disubstituted tetrazoles have been created by Esikov and co-workers [vi]. They reported that the azidating amides had certain inherent limitations. Because of the steric impact of the benzoyl substituent, N-benzoyl derivatives of amino acids nearly never react with zirconium oxychloride, sodium azide, in contrast to N-acetyl derivatives of amino acids.

A sterically hindered ortho-tetrazole group was synthesized by three separate methods, according to Duncia and co-workers. Their techniques, however, were only used to make 5-substituted-1H-tetrazoles [vii].

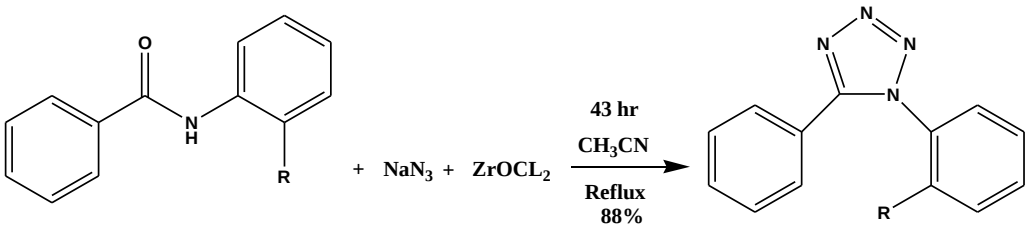
On the precursor of imidoylbenzotriazoles, Katritzky and co-workers synthesized 1,5-disubstituted tetrazoles with various substituents (aliphatic, aromatic, or heteroaromatic)[viii]. From corresponding secondary carboxamides and benzotriazoles, imidoylbenzotriazoles were made using two different techniques: oxalyl chloride and pyridine or thionyl chloride under a microwave (80 W/80$^{o}$C). These techniques, however, have two drawbacks. First off, the production of imidoylbenzotriazoles utilizing unsustainable resources involves an extra step. The only aromatic tetrazoles that are produced are para-substituted. Improved conditions for producing sterically hindered amides into their corresponding 1,5-disubstituted tetrazoles were reported by Schroeder and co-workers [ix]. Diisopropyl azodicarboxylate(DIAD),diphenylphosphoryl azide (DPPA),and diphenyl-2-pyridyl phosphine were used in THF at 45°C to achieve the best reaction conditions. However, it should be noted that this process didn't just use aliphatic amines; expensive, hazardous, and unfriendly ingredients were also used. In this article, we would like to report on the one-step, zirconium oxychloride-based synthesis of sterically hindered 1, 5-disubstituted tetrazole that Esikov and coworkers described in the presence of sodium azide. This approach has successfully overcome the above-mentioned restrictions.

## MATERIALS AND METHODS:

2-Trifluoromethyl aniline and benzoyl chloride were used for amides preparation and purchased from Merck. Sodium azide, zirconium oxychloride and acetonitrile were used for tetrazole preparation and purchased from Merck. Ethyl acetate, acetonitrle and n-hexane were purchased from Merck and used as the organic solvents. Amide 2-Trifluoromethyl aniline, as shown in Scheme 1, was prepared according to reported procedure by Ghosh and coworkers of benzoyl chloride and the corresponding aniline in solid-state [x].

**Table: The resulted product from reaction of bulky secondary amide with zirconium oxychloride and sodium azide.**

| Entry | Amide | Time (hr.) | Tetrazole | m.p. (°C) | Yield (%) |
|---|---|---|---|---|---|
| 1 | 1 | 43 | 1a | 101-102 | 88 |




**R=$CF_3$**

**scheme 1**

## INSTRUMENTATION:

The obtained tetrazole were characterized by $^{1}$H-, $^{13}$C- and $^{19}$F-NMR spectra recorded on a Bruker Avanace DRX 500 (500 MHz) using the solvent signal as reference ($CDCl_3$). The FT-

IR spectra were obtained on a Shimadzu-470 (potassium bromide tablet). The progress of the reaction and purity of the products were monitored by TLC on Kieselgel 60 $F_{254}$ plates (Merck). The eluent user petroleum etherethyl acetate 95:5, spots were visualized by UV irradiation. Melting points were recorded by an Electro Thermal 9100 and were uncorrected. HRMS spectra were obtained on Q-TOF Micromass (Wakes Inc. UK).

**PREPARATION OF HINDERED 1, 5-DISUBSTITUTED TETRAZOLE:**

Tetrazole were synthesized according to reported procedure by Esikov and co-workers. As typical procedure for [1-(2-trifluoromethan phenyl)-5-phenyl-1H-tetrazole] from amide a mixture of 2-Trifluoromethyl aniline (4 mmol), sodium azide (8 mmol) and Zirconium Oxychloride (8 mmol) in dry acetonitrile (16 ml) were refluxed and stirred with exclusion of moisture (Scheme 1). In order to determine the end of the reaction, TLC test was used to check the reaction every 6 hours. After each TLC test, 1 mmol sodium azide and 2 mmol zirconium oxychloride were added to the mixture of the reaction. The last TLC test showed the pure hindered 1, 5-disubstituted tetrazole clearly. After the completion of reaction, the mixture was poured into the saturated solution of $Na_2CO_3$ (pH ~ 7). Then the precipitate of silica was filtered. The pure products were obtained by extracting the mixture with ethyl acetate. The organic solvents (ethyl acetate and acetonitrile) were evaporated under the vacuum. The final products were kept at room temperature for more characterization.

**1-(2-Trifluoromethanphenyl)-5-phenyl-1H-tetrazole**

$^{1}$H-NMR spectrum of (500 MHz, $CDCl_3$), δ (ppm): 7.33 (t, J= 7.7 Hz, 2H), 7.41-7.43 (m, 2H), 7.49 (d, J= 7.9 Hz, 2H), 7.77 (m, 2H), 7.88-7.92 (m, 1H). $^{13}$C-NMR spectrum of (125 MHz, $CDCl_3$), δc (ppm): 154.88, 133.61, 132.18, 131.78, 131.47, 129.73, 129.02, 128.33, 128.23, 128.18, 128.16, 128.12, 127.98, 127.72, 127.47, 127.21, 125.51, 123.33, 123.04, 121.15 and 118.96, (77.32, 77.08 and 76.82 for solvent). $^{19}$F-NMR spectrum of (470 MHz, CDCl3), δF (ppm): -60.44. FT-IR (KBr) spectrum of [11]: 1099 and 1267 (-CN4 tetrazole ring), 1118 and 1140 (tetrazole ring), 1237 (Ar-F), 1287 (N-N=N), 1321 (C=N tetrazole ring), 1453 (C-H), 1504 (N=N tetrazole ring), 1584 (-N=N-), 3045 (Ar-CH) cm-1. Mass spectrum (HRMS) of (ESI) m/z: 294.8956 (M+ + 4).

**ANTIBIOTIC ACTIVITY:**

Tetrazole Compound 1a were screened for their antibacterial activity against Gram-positive bacteria viz. Bacillus subtilis (MTCC 441), Bacillus sphaericus (MTCC 11) and Staphylococcus aureus (MTCC 96), and Gram-negative bacteria viz. Pseudomonas aeruginosa (MTCC 741), Klobsinella aero genes (MTCC 39) and Chromobacterium violaceum (MTCC 2656) by disc diffusion method (NCCLS, 1982). For the antibacterial assay standard inoculums (1-2 × 107 c.f.u/mL 0.5 Mc Farland standards) were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The discs measuring 6.26 mm in diameter were prepared from Whatman no.1 filter paper and sterilized by dry heat at 140 o C for 1 h. The sterile discs previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. The plates were inverted and incubated for 24 h at 37 o C.

**Table 1 Antibiotic activity of compounds 1a**

| **Zone of inhibition at 50 µg/mL (mm)** | | | | | | |
|---|---|---|---|---|---|---|
| **Compound** | **B.subtilis** | **B.sphaericus** | **S.aureus** | **P.aeruginosa** | **K.aerogenes** | **C.violaceum** |
| **1a** | 13 | 23 | 16 | 16 | 18 | 22 |
| **Streptomycin** | 25 | 30 | 30 | 30 | 25 | 30 |

## RESULTS AND DISCUSSION:

Characterizations including $^{1}$H-, $^{13}$C-, and $^{19}$F-NMR, HRMS, and FT-IR were utilized to demonstrate the production of 1, 5-disubstituted tetrazole and antibiotic activity. TLC was used to keep an eye on the reaction's development and the product purity [xi]. To check the product purity, the melting point was utilized. Table illustrates how secondary amide 1 reacts with zirconium oxychloride and sodium azide. Azide transfer reagent was utilized with zirconium oxychloride and sodium azide. Amidate are changed into nitriles or acid azides (imidoyl azides), whilst ketones are changed into the equivalent tetrazole by rearrangement and the spread of general synthetic achieves for chemo selective formation of tetrazole derivatives [xii].

## CONCLUSIONS:

Esikov and coworkers' technique, which uses zirconium oxychloride in the presence of sodium azide and acetonitrile as a solvent, yields 88% of 1,5-disubstituted tetrazole from bulky secondary N-benzoyl amide with antibiotic activity.

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