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A ONE POT METHOD FOR THE SYNTHESIS OF 1, 5-DISUBSTITUTED TETRAZOLE CATALYZED BY EUFOD

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ABSTRACT:
A one pot method for the synthesis 1, 5-disubstituted tetrazole in 88% yields using EuFOD in the presence of sodium azide and acetonitrile as solvent. With EuFOD and Sodium Azide was used as azide transfer reagent as it transformed the amide to imidoylazide intermediate and, then, by ring closing to tetrazole. The formation of hindered 1, 5-disubstituted tetrazole was confirmed by1H-, 13C- and 19F-NMR, HRMS and FT-IR. A possible mechanism is described to clarify the effect of electron-withdrawing groups on anilines ring in the conversion to tetrazole. In fact, substituent effect on nitrogen of amide group has key role in ring closing imidoylazide intermediate to tetrazole.

KEYWORDS: 1, 5-Disubstituted tetrazole, with EuFOD and Sodium Azide, Acetonitrile, N-benzoyl amide.

INTRODUCTION:

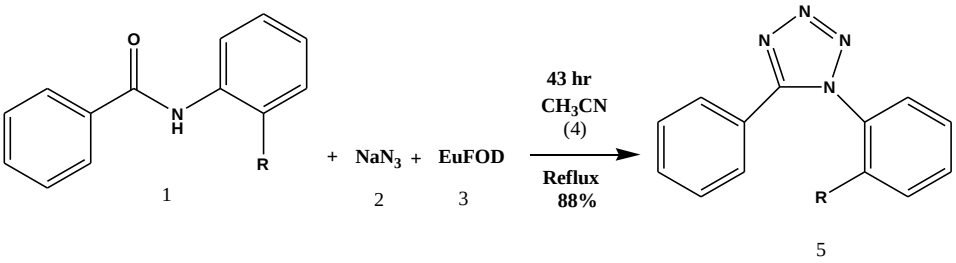
The tetrazole important in medicinal and pharmaceutical research. The class of tetrazole compounds has been recently used both as anticancer and antimicrobial agents[1]. They have received increased attention due to their potential biological activity and industrial applications [2].Furthermore, tetrazole fragment is a metabolically stable substitute for carboxy group and amide bond in the molecules of peptidomimetics [3]. The first report of amino acid derivatives containing a 5-tetrazolyl substituent were described by McManus and Herbst [4].Later, Zabrocki et al proposed the use of tetrazole 1,5-diyl fragment for the synthesis of peptidomimetics with cis-block peptide bond [5][6]. Growing demands for the synthesis of tetrazole containing peptides and peptidomimetics result in extensive studies aimed to developing effective methods for the preparation of amides derivatives containing a tetrazole moiety [7][8].

MATERIALS AND METHODS: 2-Trifluoromethyl aniline and benzoyl chloride were used for amides preparation and purchased from Merck. Sodium azide, EuFOD and acetonitrile were used for tetrazole preparation and purchased from Merck [9]. 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, were prepared according to reported procedure by Ghosh and coworkers of benzoyl chloride and the corresponding aniline in solid-state [10].

Table: The resulted product from reaction of bulky secondary amide With EuFOD and Sodium azide.

Entry	Amide	Time (hr.)	Tetrazole	m.p. (°C)	Yield (%)
1	1	43	1	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 ether-ethyl 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 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 EuFOD (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 EuFOD 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 Na2CO3 (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 [8]. The final products were kept at room temperature for more characterization.

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

1H-NMR spectrum of (500 MHz, CDCl3), 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). 13C-NMR spectrum of (125 MHz, CDCl3), 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). 19F-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).

RESULTS AND DISCUSSION:

To confirm the formation of 1, 5-disubstituted tetrazole, characterizations such as ^{1}H-, ^{13}C- and ^{19}F-NMR, HRMS and FT-IR were used. TLC was utilized to monitor the progress of the reaction and purity of the products [11]. Melting point was used to verify the purity of the product. The reaction of secondary amide 2-Trifluoromethyl aniline with EuFOD and Sodium Azide is shown in Table. With EuFOD and Sodium Azide was used as azide transfer reagent. It transforms amides to nitriles or acid azides (imidoyazides) however ketones are transformed with rearrangement into their corresponding tetrazole [12] and the spread of general synthetic achieves for chemo selective formation of tetrazole derivatives. The main question that comes in mind is that why reaction was successful with anilines containing electron-withdrawing groups in ortho position and unsuccessful with anilines containing electronreleasing groups such as 2-methyl, 2-ethyl, 2-sec-butyl and 2-methoxy aniline.

CONCLUSIONS:

In this paper, a one-step method is reported for synthesis of 1,5-disubstituted tetrazole from bulky secondary N-benzoyl amides in 88% yield by Esikov and co-workers method using EuFOD in the presence of sodium azide and acetonitrile as a solvent.

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