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Microwave-assisted synthesis of 1-aryl-5-(trifluoromethyl)-1H-tetrazoles

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ABSTRACT

This general protocol provides a wide variety of 5-substituted-1H-tetrazoles in good yields under mild reaction conditions. An efficient, green, and convenient method for the preparation of new 5-substituted-tetrazoles via microwave-assisted 1,3-dipolar cycloaddition reaction of *N*-aryl-2,2,2-trifluoroacetimidoyl chlorides and sodium azide in acetonitrile without assistance of any catalyst has been reported. The FT-IR, ^{19}F NMR, ^{1}H NMR, ^{13}C NMR, HMBC spectra, elemental analysis, and single-crystal X-ray analysis confirm the structures of the products.

1. Introduction

Tetrazoles are a class of heterocycles with a wide range of applications that are receiving considerable attention. This functional group has a role in coordination chemistry as ligands, in materials science as specialty explosives and information recording systems, as good potential inhibitors, and as intermediates in a variety of synthetic transformations [1–3]. Moreover, the tetrazole groups have found use in pharmaceuticals as lipophilic spacers and carboxylic acid surrogates. Also the tetrazole ring appears in some well-known drugs [4]. The outstanding achievements of the pharmaceutical chemistry in the last decade are due in no small way to the creation of novel drugs containing a tetrazole ring as structural fragment. Tetrazoles have not been found in nature. With rare exceptions these compounds do not exhibit appreciable biological activity, but they are at the same time resistant to biological degradation. It is this property that makes it possible to use tetrazoles as isosteric substituents of various functional groups in the development of biologically active substances [5]. Therefore, a number of methods have been reported for the preparation of tetrazoles [6]. One of the major synthetic routes to tetrazole formation is the [2 + 3] cycloaddition of an organonitrile and an azide salt [7–9].

However, many of these protocols have some disadvantages, such as the use of toxic metals, strong Lewis acid, expensive reagents, low yield, harsh reaction conditions, water sensitivity, and the presence of hydrazoic acid, which is toxic and explosive. Thus, the development of a convenient and safe process for the preparation of new tetrazole derivatives containing fluorine atom is an interesting subject for investigation.

Microwave irradiation has long been considered as a green technology because it often allows solvent-free reactions and its level of energy consumption is low compared with more traditional methods [10–17].

The short reaction time and expanded reaction range offered by microwave-assisted organic synthesis are suited to the increased demands in industry. In particular, there is a requirement in the pharmaceutical industry for a higher number of novel chemical entities to be produced, which requires chemists to employ a number of resources to reduce the time for the production of compounds.

Although there are many methods for the preparation of tetrazole compounds; and the synthesis of different tetrazole derivatives have been reported in literature, but there are a few reports for synthesis of their trifluoromethylated derivatives [18]. In continuing of our studies [19–21], we now report synthesis of 1-aryl-5-(trifluoromethyl)-1H-tetrazoles derivatives using reaction of trifluoroacetimidoyl chloride derivatives with sodium azide in acetonitrile by two methods: (a) in acetonitrile at room temperature and (b) in acetonitrile using microwave irradiation, in one pot reaction.

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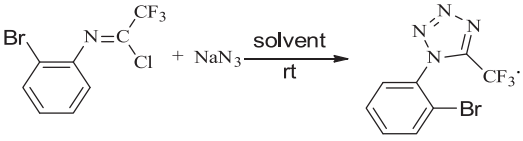
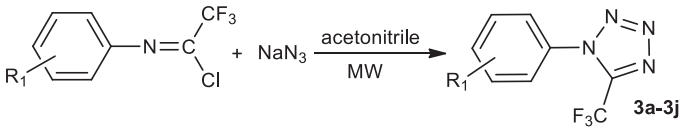
Table 1
Model reaction, conditions, and yield.



Entry	Solvent	Conditions	Yield (%)
1	CH_3CN	RT, 7 h	78
2	THF	RT, 7 h	56
3	Toluene	RT, 7 h	43
4	CH_2Cl_2	RT, 7 h	46
5	DMF	RT, 7 h	31
6	H_2O	RT, 7 h	No reaction

2. Results and discussion

Trifluoromethylated tetrazoles are very important due to the various and high biological properties. In this research, to increase the interesting and remarkable biological activities of tetrazoles, we require the synthesis of the tetrazole-annulated trifluoromethyl derivative with the following structure (see Scheme 1).

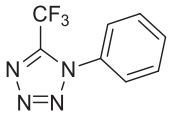
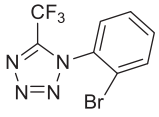
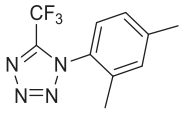
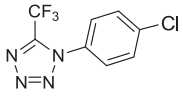
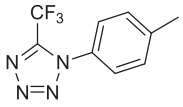
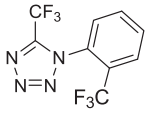
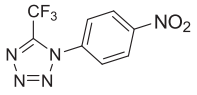
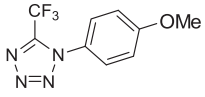
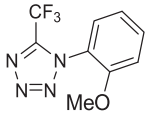
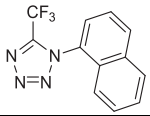


Scheme 1. Synthesis of trifluoromethylated tetrazoles derivatives.

In this research, imidoyl halides are obtained via refluxing a mixture of trifluoroacetic acid and a primary amine in carbon tetrachloride in the presence of triethylamine and triphenylphosphine [21,22]. A variety of acetymidoyl chlorides were examined to generate the desired coupled products.

New 5-substituted-tetrazoles via microwave-assisted 1,3-dipolar cycloaddition reaction of *N*-aryl-2,2,2-trifluoroacetimidoyl chlorides and sodium azide in acetonitrile without using any

Table 2
Synthesis of 1-aryl-5-(trifluoromethyl)-1H-tetrazoles **3a**–**3j**.

Compound	R_1	Product	Room temperature		Microwave condition		Melting point (°C)
			Time	Isolated yield (%)	Microwave irradiation time (min)	Isolated yield (%)	
3a	H		6	84	10	95	Yellow oil
3b	2-Br		7	78	10	92	63–64
3c	2,4-dimethy		7	76	10	90	Yellow oil
3d	4-Cl		6	78	10	95	Yellow oil
3e	4-CH3		8	69	9	94	Yellow oil[23]
3f	2-CF_3		7	68	8	97	73–74
3g	4-NO_2		8	71	8	96	70–71
3h	4-OCH_3		8	75	10	94	Yellow oil
3i	2-OCH_3		8	76	10	94	Yellow liquid
3j	Naphthalene		8	78	10	95	105–106

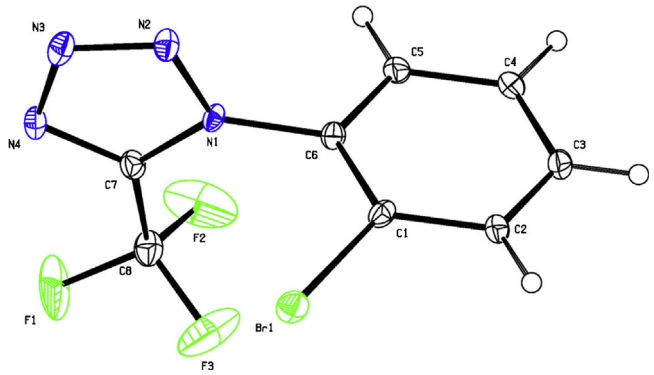


Fig. 1. The ORTEP diagram of **3b**. Thermal ellipsoids are at 30% probability level.

catalysts have been reported. Organic solvents are very important as liquid medium for reactions to take place, and after the synthesis of a chemical product for extraction, separation, purification, and drying. In search of an effective solvent and to optimize the experimental conditions, the reaction of *N*-(2-bromophenyl)-2,2,2-trifluoroacetimidoyl chloride and sodium azide was considered as the model reaction, reaction was carried out with magnetic stirring for 7 h at room temperature (Table 1). The reaction in CH_3CN proceeded in excellent yield (entry 1). On the other hand, the reactions in THF, toluene, CH_2Cl_2, and DMF resulted in moderate and insufficient yields (entries **2**–**5**). We then examined the generality of the reaction in CH_3CN. As a refinement of our method, we next sought to carry out the reaction under microwave irradiation. As shown in Table 2, these reactions normally proceeded in improved yields compared to the previous method, and with the obvious advantage of a faster and more convenient operation. As summarized in Table 2, a variety of substituents, both electron withdrawing and electron releasing, could be accommodated without significant differences in reaction time or yield. Besides the much milder conditions and shortened reaction times, our method also represents a considerable improvement in yield. Another advantage of this reaction is easy purification of products without using chromatography or recrystallization. The crude product was simply washed with *n*-hexane for purification. This is an important advantage to reduce costs in industry. The present study revealed the results using a wide variety of imidoyl chloride a straightforward procedure with much milder conditions, shortened reaction times, simple purification, and a high yield.

X-ray crystallographic analysis revealed the structure of compound **3b** as depicted in Fig. 1.

3. X-ray crystallography

X-ray data for **3b:** $C_8H_4N_4BrF_3$, $M = 293.05$, orthorhombic system, space group $P2_12_12_1$, $a = 6.0152(12)$, $b = 9.3822(19)$, $c = 17.933(4)$ Å; $V = 1012.1(4)$ Å^3, $Z = 4$, $D_{calcd} = 1.923$ g cm^{-3}, μ(Mo–Kα) = 4.082 mm^{-1}, crystal dimension of 0.40 × 0.35 × 0.35 mm. The X-ray diffraction measurement was made on a STOE IPDS-*2T* diffractometer with graphite monochromated Mo–Kα radiation. The structure was solved by using SHELXS.

The data reduction and structure refinement was carried out with SHELXL using the X-STEP32 crystallographic software package. The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final $R_1 = 0.0684$, $wR_2 = 0.1481$, and $S = 1.026$ with 145 parameters using 2657 independent reflection (θ range = 3.14–29.14°). Hydrogen atoms were added in idealized positions. The crystallographic information file has been deposited with the Cambridge Data Centre, CCDC 1006291. *X-STEP32 Version 1.07b*, *Crystallographic Package*; Stoe & Cie GmbH: Darmstadt, Germany, 2000.

4. Conclusion

In conclusion, we described a microwave-assisted 1,3-dipolar cycloaddition reaction for the synthesis of trifluoromethylated tetrazole derivatives in the absence of any catalyst. The use of microwave conditions not only made the reaction feasible, but also added additional beneficial features to the reaction such as shortened reaction time. This new process provided an environmentally useful conventional organic solvent, easy work up, and reduced waste production by the lack of catalysts or additive agents.

5. Experimental

5.1. General methods

Ethos 1 advanced Microwave Digestion system Milestone was used for synthesis of compounds. Melting points were determined on a Melt-Tem II melting point apparatus and are uncorrected. IR spectra were obtained on a Matson-1000 FT-IR spectrometer. Peaks are reported in wave numbers (cm^{-1}). All of the NMR spectra were recorded on a Bruker model DRX-300 AVANCE (^{1}H: 300 ^{13}C: 75, ^{19}F: 235 MHz) NMR spectrometer. Chemical shifts of ^{1}H and ^{13}C NMR are reported in parts per million (ppm) from tetramethylsilane (TMS) as an internal standard in DMSO-d6 or $CDCl_3$ as a solvent and ^{19}F NMR are reported in parts per million (ppm) from $CFCl_3$ as an internal standard in DMSO-d6 or $CDCl_3$ as a solvent. The crystallographic information file has been deposited with the Cambridge Data Centre, CCDC 1006291.

BB. *X-STEP32 Version 1.07b*, *Crystallographic Package*; Stoe & Cie GmbH: Darmstadt, Germany, 2000.

5.2. General procedure A

A mixture of acetimidoyl chloride (1 mmol), sodium azide (1 mmol), and acetonitrile (5 mL) was stirred at room temperature for appropriate time (6–8 h), after completion of the reaction, as indicated by TLC, the reaction mixture was filtered. After removing the solvent under reduced pressure, if necessary, the crude products were purified by washing with *n*-hexane to give the target product **3a–3j** (69–84%).

5.3. General procedure B

A mixture of acetimidoyl chloride (1 mmol), sodium azide (1 mmol), and acetonitrile (3 mL) was irradiated in a microwave oven at 300 W for 8–10 min, after completion of the reaction, as indicated by TLC, the reaction mixture was filtered. After removing the solvent under reduced pressure, if necessary, the crude products were purified by washing with *n*-hexane to give the target product **3a–3j** (90–95%).

5.4. Characterization

5.4.1. 1-phenyl-5-(trifluoromethyl)-1H-tetrazole (3a)

Prepared according to General Procedure A and B, pale yellow oil, (yield: 95%). IR (neat, cm^{-1}): 3071, 1531, 1499, ^{1}H NMR (DMSO, 300 MHz) δ 7.72–7.78 (m, 2 H), 7.70–7.74 (m, 3 H), ^{13}C NMR (DMSO, 75 MHz): δ 145.90 (q, J = 42.0 Hz), 132.41, 131.59, 131.58, 129.79, 129.76, 125.05, 117.73 (q, J = 270.0 Hz), ^{19}F NMR (DMSO, 235 MHz) δ 59.78 ppm. Elemental analysis: value calculated for $C_8H_5F_3N_4$: C, 44.87%; H, 2.35%; N, 26.16%; value found: C, 44.47%; H, 2.24%; N, 26.55%.

5.4.2. 1-(2-bromophenyl)-5-(trifluoromethyl)-1H-tetrazole (3b)

Prepared according to General Procedure A and B, white powder, m.p = 63–64 °C (yield: 92%). IR (neat, cm^{-1}): 3080, 1537,

1490. ^{1}H NMR (DMSO, 300 MHz): δ 8.04–8.01 (m, 2 H), 7.76–7.69 (m, 2 H). Elemental analysis: value calculated for $C_8H_4BrF_3N_4$: C, 32.79%; H, 1.38%; N, 19.12%; value found: C, 32.54%; H, 1.44%; N, 19.35%.

5.4.3. 1-(2,4-dimethylphenyl)-5-(trifluoromethyl)-1H-tetrazole(3c)

Prepared according to General Procedure A and B, yellow oil, IR (neat, cm^{-1}): 3091, 1543, and 1487. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.17, 2.30(s, 6H, CH_3), 7.02–7.20(m, 3 H, Ar). Elemental analysis: value calculated for chemical formula: $C_{10}H_9F_3N_4$: C, 49.59%; H, 3.75%; N, 23.13%; value found C, 49.21%; H, 3.88%; N, 23.44%.

5.4.4. 1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-tetrazole (3d)

Prepared according to General Procedure A and B, pale yellow oil (yield: 92.2%). IR (neat, cm^{-1}): 3101, 1531, and 1497. ^{1}H NMR (DMSO, 300 MHz): δ 7.60–7.56 (m, 2 H), 7.47–7.43 (m, 2 H). ^{13}C NMR (DMSO, 75 MHz): δ 146.02 (q, J = 42.0 Hz), 138.13, 130.94, 130.25, 126.48, 117.75 (q, J = 270.9 Hz). Elemental analysis: value calculated for $C_8H_4ClF_3N_4$: C, 38.65%; H, 1.62%; N, 22.93%; value found: C, 38.51%; H, 1.74%; N, 22.40%.

5.4.5. 1-(4-methylphenyl)-5-(trifluoromethyl)-1H-tetrazole (3e)

Prepared according to General Procedure A and B, pale yellow oil (yield: 97.3%). IR (neat, cm^{-1}): 3045, 2930, 1531, and 1514. ^{1}H NMR (DMSO, 300 MHz): δ 7.37–7.31 (m, 4 H), 2.42 (s, 3 H). ^{13}C NMR (DMSO, 75 MHz): δ 145.96 (q, J = 41.2 Hz), 142.28, 130.33, 129.95, 124.83, 117.81 (q, J = 270.9 Hz), 21.10. Elemental analysis: value calculated for $C_9H_7F_3N_4$: C, 47.37%; H, 3.09%; N, 24.98%; value found: C, 46.89%; H, 2.63%; N, 24.64%

5.4.6. 1-(2-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-1H-tetrazole (3f)

Prepared according to General Procedure A and B, white powder m.p. = 73–74 °C (yield: 97%). IR (neat, cm^{-1}): 3091, 1612, and 1547, ^{1}H NMR (DMSO, 300 MHz): δ 8.22–8.16 (m, 2 H), 8.01–8.05 (m, 2 H). ^{13}C NMR (DMSO, 75 MHz): δ 135.12, 134.14, 130.62, 129.25, 28.63, 128.55, 124.97, 120.63, 120.09, 115.76. Elemental analysis: value calculated for $C_9H_4F_6N_4$: C, 38.31%; H, 1.43%; N, 19.86%; value found: C, 38.12%; H, 1.58%; N, 19.73%.

5.4.7. 1-(4-nitrophenyl)-5-(trifluoromethyl)-1H-tetrazole(3g)

Prepared according to General Procedure A and B, white powder, m.p. = 70–71?C (yield: 97%). IR (neat, cm-1): 3091, 1612, and 1547, ^{1}H NMR (DMSO, 300 MHz): δ 8.56–8.53 (d, J = 8.7 Hz, 2H), 8.01–8.05 (d, J = 8.4 Hz, 2H). Elemental analysis: value calculated for $C_8H_4F_3N_5O_2$: C, 37.08%; H, 1.56%; N, 27.02%; value found: C, 37.21%; H, 1.54%; N, 27.21%.

5.4.8. 1-(4-methoxyphenyl)-5-(trifluoromethyl)-1H-tetrazole (3h)

Prepared according to General Procedure A and B, pale yellow oil (yield: 98.3%). IR (neat, cm^{-1}): 1609, 1533, 1514, and 1466. ^{1}H NMR (DMSO, 300 MHz): δ 7.38 (d, J = 8.7 Hz, 2 H), 7.06 (d, J = 8.7 Hz, 2 H), 3.89 (s, 3 H). ^{13}C NMR (DMSO, 75 MHz): δ 161. 72, 146.03 (q, J = 42.1 Hz), 126.51, 124.95, 117.81 (q, J = 270.6 Hz), 114.87, 55.72. Elemental analysis: value calculated for $C_9H_7F_3N_4O$: C, 44.27%; H, 2.89%; N, 22.95%; value found: C, 43.81%; H, 2.81%; N, 22.35%.

5.4.9. 1-(2-methoxyphenyl)-5-(trifluoromethyl)-1H-tetrazole (3i)

Prepared according to General Procedure A and B, pale yellow oil (yield: 97.6%)._IR (neat, cm^{-1}): 1601, 1563, 1506, and 1470. ^{1}H NMR (DMSO, 300 MHz): δ 7.59 (ddd, J = 7.8, 7.5, 1.7 Hz, 1 H), 7.36 (dd, J = 7.8, 1.7 Hz, 1 H), 7.14-7.08 (m, 2 H), 3.79 (s, 3H). ^{13}C NMR (DMSO, 75 MHz): δ 153.55, 147.00 (q, J = 41.5 Hz), 133.19, 127.22, 121.00, 120.59, 117.60 (q, J = 270.4 Hz), 112.07, 55.76. Elemental analysis: value calculated for $C_9H_7F_3N_4O$: C, 44.27%; H, 2.89%; N, 22.95%; value found: C, 44.35%; H, 3.18%; N, 23.05%.

5.4.10. 1-(naphthalen-1-yl)-5-(trifluoromethyl)-1H-tetrazole (3j)

Prepared according to General Procedure A and B, white powder, m.p. = 105–106 °C (yield: 94.1%). IR (KBr, cm^{-1}): 3067, 1599, and 1531. ^{1}H NMR (DMSO, 300 MHz): δ 8.11 (d, J = 8.3 Hz, 1H) 7.96 (d, J = 8.3 Hz, 1H), 7.62–7.50 (m, 4H), 7.02 (d, J = 8.3 Hz, 1H). ^{13}C NMR (DMSO, 75 MHz): δ 147.68 (q, J = 42.0 Hz), 133. 91, 132.55, 128.81, 128.73, 128.46, 128.40, 127.64, 125.10, 124.63, 120.74, 117.74 (q, J = 270.9 Hz). Elemental analysis: value calculated for $C_{12}H_7F_3N_4$: C, 54.55%; H, 2.67%; N, 21.21%; value found: C, 54.27%; H, 2.66%; N, 21.21%.

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